

polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to modulate IgE concentrations in vitro or in vivo.

Moreover, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention have uses in the diagnosis, prognosis, prevention, and/or treatment of inflammatory conditions. For example, since polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists of the invention may inhibit the activation, proliferation and/or differentiation of cells involved in an inflammatory response, these molecules can be used to prevent and/or treat chronic and acute inflammatory conditions. Such inflammatory conditions include, but are not limited to, for example, inflammation associated with infection (e.g., septic shock, sepsis, or systemic inflammatory response syndrome), ischemia-reperfusion injury, endotoxin lethality, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, inflammatory bowel disease, Crohn's disease, over production of cytokines (e.g., TNF or IL-1), respiratory disorders (e.g., asthma and allergy); gastrointestinal disorders (e.g., inflammatory bowel disease); cancers (e.g., gastric, ovarian, lung, bladder, liver, and breast); CNS disorders (e.g., multiple sclerosis; ischemic brain injury and/or stroke, traumatic brain injury, neurodegenerative disorders (e.g., Parkinson's disease and Alzheimer's disease); AIDS-related dementia; and prion disease); cardiovascular disorders (e.g., atherosclerosis, myocarditis, cardiovascular disease, and cardiopulmonary bypass complications); as well as many additional diseases, conditions, and disorders that are characterized by inflammation (e.g., hepatitis, rheumatoid arthritis, gout, trauma, pancreatitis, sarcoidosis, dermatitis, renal ischemia-reperfusion injury, Grave's disease, systemic lupus erythematosus, diabetes mellitus, and allogenic transplant rejection).

Because inflammation is a fundamental defense mechanism, inflammatory disorders can effect virtually any tissue of the body. Accordingly, polynucleotides, polypeptides, and antibodies of the invention, as well as agonists or antagonists thereof, have uses in the treatment of tissue-specific inflammatory disorders, including, but not limited to, adrenalitis, alveolitis, angiocholecystitis, appendicitis, balanitis, blepharitis, bronchitis, bursitis, carditis, cellulitis, cervicitis, cholecystitis, chondritis, cochlitis, colitis, conjunctivitis, cystitis, dermatitis, diverticulitis,

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encephalitis, endocarditis, esophagitis, eustachitis, fibrositis, folliculitis, gastritis, gastroenteritis, gingivitis, glossitis, hepatosplenitis, keratitis, labyrinthitis, laryngitis, lymphangitis, mastitis, media otitis, meningitis, metritis, mucitis, myocarditis, myositis, myringitis, nephritis, neuritis, orchitis, osteochondritis, otitis, pericarditis, peritendonitis, peritonitis, pharyngitis, phlebitis, poliomyelitis, prostatitis, pulpitis, retinitis, rhinitis, salpingitis, scleritis, sclerochoroiditis, scrotitis, sinusitis, spondylitis, steatitis, stomatitis, synovitis, syringitis, tendonitis, tonsillitis, urethritis, and vaginitis.

In specific embodiments, polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, are useful to diagnose, prognose, prevent, and/or treat organ transplant rejections and graft-versus-host disease. Organ rejection occurs by host immune cell destruction of the transplanted tissue through an immune response. Similarly, an immune response is also involved in GVHD, but, in this case, the foreign transplanted immune cells destroy the host tissues.

Polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, that inhibit an immune response, particularly the activation, proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing organ rejection or GVHD. In specific embodiments, polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, that inhibit an immune response, particularly the activation, proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing experimental allergic and hyperacute xenograft rejection.

In other embodiments, polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, are useful to diagnose, prognose, prevent, and/or treat immune complex diseases, including, but not limited to, serum sickness, post streptococcal glomerulonephritis, polyarteritis nodosa, and immune complex-induced vasculitis.

Polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the invention can be used to treat, detect, and/or prevent infectious agents. For example, by increasing the immune response, particularly increasing the proliferation activation and/or differentiation of B and/or T cells, infectious diseases may be treated, detected, and/or prevented. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively,

polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may also directly inhibit the infectious agent (refer to section of application listing infectious agents, etc), without necessarily eliciting an immune response.

5 In another embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a vaccine adjuvant that enhances immune responsiveness to an antigen. In a specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an adjuvant to enhance tumor-specific immune responses.

10 In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an adjuvant to enhance anti-viral immune responses. Anti-viral immune responses that may be enhanced using the compositions of the invention as an adjuvant, include virus and virus associated diseases or symptoms described herein or otherwise known in the art.

15 In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a virus, disease, or symptom selected from the group consisting of: AIDS, meningitis, Dengue, EBV, and hepatitis (e.g., hepatitis B). In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to a virus, disease, or symptom selected
20 from the group consisting of: HIV/AIDS, respiratory syncytial virus, Dengue, rotavirus, Japanese B encephalitis, influenza A and B, parainfluenza, measles, cytomegalovirus, rabies, Junin, Chikungunya, Rift Valley Fever, herpes simplex, and yellow fever.

 In another specific embodiment, polypeptides, antibodies, polynucleotides
25 and/or agonists or antagonists of the present invention are used as an adjuvant to enhance anti-bacterial or anti-fungal immune responses. Anti-bacterial or anti-fungal immune responses that may be enhanced using the compositions of the invention as an adjuvant, include bacteria or fungus and bacteria or fungus associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments,
30 the compositions of the invention are used as an adjuvant to enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group consisting of: tetanus, Diphtheria, botulism, and meningitis type B.

In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group consisting of: *Vibrio cholerae*, *Mycobacterium leprae*, *Salmonella typhi*, *Salmonella paratyphi*, *Meisseria meningitidis*,
5 *Streptococcus pneumoniae*, Group B streptococcus, *Shigella spp.*, Enterotoxigenic *Escherichia coli*, Enterohemorrhagic *E. coli*, and *Borrelia burgdorferi*.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an adjuvant to enhance anti-parasitic immune responses. Anti-parasitic immune responses that may
10 be enhanced using the compositions of the invention as an adjuvant, include parasite and parasite associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a parasite. In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an
15 immune response to Plasmodium (malaria) or Leishmania.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may also be employed to treat infectious diseases including silicosis, sarcoidosis, and idiopathic pulmonary fibrosis; for example, by preventing the recruitment and activation of mononuclear
20 phagocytes.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an antigen for the generation of antibodies to inhibit or enhance immune mediated responses against polypeptides of the invention.

25 In one embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are administered to an animal (e.g., mouse, rat, rabbit, hamster, guinea pig, pigs, micro-pig, chicken, camel, goat, horse, cow, sheep, dog, cat, non-human primate, and human, most preferably human) to boost the immune system to produce increased quantities of one or more antibodies (e.g., IgG, IgA, IgM, and IgE), to induce higher affinity antibody production and
30 immunoglobulin class switching (e.g., IgG, IgA, IgM, and IgE), and/or to increase an immune response.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a stimulator of B cell responsiveness to pathogens.

5 In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an activator of T cells.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent that elevates the immune status of an individual prior to their receipt of
10 immunosuppressive therapies.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to induce higher affinity antibodies.

15 In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to increase serum immunoglobulin concentrations.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to accelerate recovery of immunocompromised individuals.

20 In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to boost immunoresponsiveness among aged populations and/or neonates.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an immune system
25 enhancer prior to, during, or after bone marrow transplant and/or other transplants (e.g., allogeneic or xenogeneic organ transplantation). With respect to transplantation, compositions of the invention may be administered prior to, concomitant with, and/or after transplantation. In a specific embodiment, compositions of the invention are administered after transplantation, prior to the
30 beginning of recovery of T-cell populations. In another specific embodiment, compositions of the invention are first administered after transplantation after the

beginning of recovery of T cell populations, but prior to full recovery of B cell populations.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to boost
5 immunoresponsiveness among individuals having an acquired loss of B cell function. Conditions resulting in an acquired loss of B cell function that may be ameliorated or treated by administering the polypeptides, antibodies, polynucleotides and/or agonists or antagonists thereof, include, but are not limited to, HIV Infection, AIDS, bone marrow transplant, and B cell chronic lymphocytic leukemia (CLL).

10 In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to boost immunoresponsiveness among individuals having a temporary immune deficiency. Conditions resulting in a temporary immune deficiency that may be ameliorated or treated by administering the polypeptides, antibodies, polynucleotides and/or agonists
15 or antagonists thereof, include, but are not limited to, recovery from viral infections (e.g., influenza), conditions associated with malnutrition, recovery from infectious mononucleosis, or conditions associated with stress, recovery from measles, recovery from blood transfusion, and recovery from surgery.

In another specific embodiment, polypeptides, antibodies, polynucleotides
20 and/or agonists or antagonists of the present invention are used as a regulator of antigen presentation by monocytes, dendritic cells, and/or B-cells. In one embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention enhance antigen presentation or antagonizes antigen presentation in vitro or in vivo. Moreover, in related embodiments, said enhancement
25 or antagonism of antigen presentation may be useful as an anti-tumor treatment or to modulate the immune system.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to direct an individual's immune system towards development of a humoral response (i.e.
30 TH2) as opposed to a TH1 cellular response.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means to induce

tumor proliferation and thus make it more susceptible to anti-neoplastic agents. For example, multiple myeloma is a slowly dividing disease and is thus refractory to virtually all anti-neoplastic regimens. If these cells were forced to proliferate more rapidly their susceptibility profile would likely change.

5 In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a stimulator of B cell production in pathologies such as AIDS, chronic lymphocyte disorder and/or Common Variable Immunodeficiency.

10 In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a therapy for generation and/or regeneration of lymphoid tissues following surgery, trauma or genetic defect. In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used in the pretreatment of bone marrow samples prior to transplant.

15 In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a gene-based therapy for genetically inherited disorders resulting in immuno-incompetence/immunodeficiency such as observed among SCID patients.

20 In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means of activating monocytes/macrophages to defend against parasitic diseases that effect monocytes such as Leishmania.

25 In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means of regulating secreted cytokines that are elicited by polypeptides of the invention.

 In another embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used in one or more of the applications described herein, as they may apply to veterinary medicine.

30 In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means of blocking various aspects of immune responses to foreign agents or self. Examples of diseases or conditions in which blocking of certain aspects of immune responses may

be desired include autoimmune disorders such as lupus, and arthritis, as well as immunoresponsiveness to skin allergies, inflammation, bowel disease, injury and diseases/disorders associated with pathogens.

5 In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a therapy for preventing the B cell proliferation and Ig secretion associated with autoimmune diseases such as idiopathic thrombocytopenic purpura, systemic lupus erythematosus and multiple sclerosis.

10 In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a inhibitor of B and/or T cell migration in endothelial cells. This activity disrupts tissue architecture or cognate responses and is useful, for example in disrupting immune responses, and blocking sepsis.

15 In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a therapy for chronic hypergammaglobulinemia evident in such diseases as monoclonal gammopathy of undetermined significance (MGUS), Waldenstrom's disease, related idiopathic monoclonal gammopathies, and plasmacytomas.

20 In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may be employed for instance to inhibit polypeptide chemotaxis and activation of macrophages and their precursors, and of neutrophils, basophils, B lymphocytes and some T-cell subsets, e.g., activated and CD8 cytotoxic T cells and natural killer cells, in certain autoimmune and chronic inflammatory and infective diseases. Examples of autoimmune diseases are described
25 herein and include multiple sclerosis, and insulin-dependent diabetes.

The polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may also be employed to treat idiopathic hyper-eosinophilic syndrome by, for example, preventing eosinophil production and migration.

30 In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used to enhance or inhibit complement mediated cell lysis.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used to enhance or inhibit antibody dependent cellular cytotoxicity.

5 In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may also be employed for treating atherosclerosis, for example, by preventing monocyte infiltration in the artery wall.

10 In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may be employed to treat adult respiratory distress syndrome (ARDS).

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may be useful for stimulating wound and tissue repair, stimulating angiogenesis, and/or stimulating the repair of vascular or lymphatic diseases or disorders. Additionally, agonists and antagonists of
15 the invention may be used to stimulate the regeneration of mucosal surfaces.

In a specific embodiment, polynucleotides or polypeptides, and/or agonists thereof are used to diagnose, prognose, treat, and/or prevent a disorder characterized by primary or acquired immunodeficiency, deficient serum immunoglobulin production, recurrent infections, and/or immune system dysfunction. Moreover,
20 polynucleotides or polypeptides, and/or agonists thereof may be used to treat or prevent infections of the joints, bones, skin, and/or parotid glands, blood-borne infections (e.g., sepsis, meningitis, septic arthritis, and/or osteomyelitis), autoimmune diseases (e.g., those disclosed herein), inflammatory disorders, and malignancies, and/or any disease or disorder or condition associated with these infections, diseases,
25 disorders and/or malignancies) including, but not limited to, CVID, other primary immune deficiencies, HIV disease, CLL, recurrent bronchitis, sinusitis, otitis media, conjunctivitis, pneumonia, hepatitis, meningitis, herpes zoster (e.g., severe herpes zoster), and/or pneumocystis carinii. Other diseases and disorders that may be prevented, diagnosed, prognosed, and/or treated with polynucleotides or
30 polypeptides, and/or agonists of the present invention include, but are not limited to, HIV infection, HTLV-BLV infection, lymphopenia, phagocyte bactericidal dysfunction anemia, thrombocytopenia, and hemoglobinuria.

In another embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention are used to treat, and/or diagnose an individual having common variable immunodeficiency disease ("CVID"; also known as "acquired agammaglobulinemia" and "acquired hypogammaglobulinemia") or a subset of this disease.

In a specific embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to diagnose, prognose, prevent, and/or treat cancers or neoplasms including immune cell or immune tissue-related cancers or neoplasms. Examples of cancers or neoplasms that may be prevented, diagnosed, or treated by polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention include, but are not limited to, acute myelogenous leukemia, chronic myelogenous leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, acute lymphocytic anemia (ALL) Chronic lymphocyte leukemia, plasmacytomas, multiple myeloma, Burkitt's lymphoma, EBV-transformed diseases, and/or diseases and disorders described in the section entitled "Hyperproliferative Disorders" elsewhere herein.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a therapy for decreasing cellular proliferation of Large B-cell Lymphomas.

In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means of decreasing the involvement of B cells and Ig associated with Chronic Myelogenous Leukemia.

In specific embodiments, the compositions of the invention are used as an agent to boost immunoresponsiveness among B cell immunodeficient individuals, such as, for example, an individual who has undergone a partial or complete splenectomy.

Antagonists of the invention include, for example, binding and/or inhibitory antibodies, antisense nucleic acids, ribozymes or soluble forms of the polypeptides of the present invention (e.g., Fc fusion protein; see, e.g., Example 9). Agonists of the invention include, for example, binding or stimulatory antibodies, and soluble forms of the polypeptides (e.g., Fc fusion proteins; see, e.g., Example 9). polypeptides,

antibodies, polynucleotides and/or agonists or antagonists of the present invention may be employed in a composition with a pharmaceutically acceptable carrier, e.g., as described herein.

In another embodiment, polypeptides, antibodies, polynucleotides and/or
5 agonists or antagonists of the present invention are administered to an animal
(including, but not limited to, those listed above, and also including transgenic
animals) incapable of producing functional endogenous antibody molecules or having
an otherwise compromised endogenous immune system, but which is capable of
producing human immunoglobulin molecules by means of a reconstituted or partially
10 reconstituted immune system from another animal (see, e.g., published PCT
Application Nos. WO98/24893, WO/9634096, WO/9633735, and WO/9110741).
Administration of polypeptides, antibodies, polynucleotides and/or agonists or
antagonists of the present invention to such animals is useful for the generation of
monoclonal antibodies against the polypeptides, antibodies, polynucleotides and/or
15 agonists or antagonists of the present invention in an organ system listed above.

Blood-Related Disorders

The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists
of the present invention may be used to modulate hemostatic (the stopping of
20 bleeding) or thrombolytic (clot dissolving) activity. For example, by increasing
hemostatic or thrombolytic activity, polynucleotides or polypeptides, and/or agonists
or antagonists of the present invention could be used to treat or prevent blood
coagulation diseases, disorders, and/or conditions (e.g., afibrinogenemia, factor
deficiencies, hemophilia), blood platelet diseases, disorders, and/or conditions (e.g.,
25 thrombocytopenia), or wounds resulting from trauma, surgery, or other causes.
Alternatively, polynucleotides, polypeptides, antibodies, and/or agonists or
antagonists of the present invention that can decrease hemostatic or thrombolytic
activity could be used to inhibit or dissolve clotting. These molecules could be
important in the treatment or prevention of heart attacks (infarction), strokes, or
30 scarring.

In specific embodiments, the polynucleotides, polypeptides, antibodies, and/or
agonists or antagonists of the present invention may be used to prevent, diagnose,

prognose, and/or treat thrombosis, arterial thrombosis, venous thrombosis, thromboembolism, pulmonary embolism, atherosclerosis, myocardial infarction, transient ischemic attack, unstable angina. In specific embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used for the prevention of occlusion of saphenous grafts, for reducing the risk of periprocedural thrombosis as might accompany angioplasty procedures, for reducing the risk of stroke in patients with atrial fibrillation including nonrheumatic atrial fibrillation, for reducing the risk of embolism associated with mechanical heart valves and or mitral valves disease. Other uses for the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention, include, but are not limited to, the prevention of occlusions in extracorporeal devices (e.g., intravascular canulas, vascular access shunts in hemodialysis patients, hemodialysis machines, and cardiopulmonary bypass machines).

In another embodiment, a polypeptide of the invention, or polynucleotides, antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to prevent, diagnose, prognose, and/or treat diseases and disorders of the blood and/or blood forming organs associated with the tissue(s) in which the polypeptide of the invention is expressed, including one, two, three, four, five, or more tissues disclosed in Table 1B, column 8 (Tissue Distribution Library Code).

The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to modulate hematopoietic activity (the formation of blood cells). For example, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to increase the quantity of all or subsets of blood cells, such as, for example, erythrocytes, lymphocytes (B or T cells), myeloid cells (e.g., basophils, eosinophils, neutrophils, mast cells, macrophages) and platelets. The ability to decrease the quantity of blood cells or subsets of blood cells may be useful in the prevention, detection, diagnosis and/or treatment of anemias and leukopenias described below. Alternatively, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to decrease the quantity of all or subsets of blood cells, such as, for example, erythrocytes, lymphocytes (B or T cells), myeloid cells (e.g.,

basophils, eosinophils, neutrophils, mast cells, macrophages) and platelets.. The ability to decrease the quantity of blood cells or subsets of blood cells may be useful in the prevention, detection, diagnosis and/or treatment of leukocytoses, such as, for example eosinophilia.

5 The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to prevent, treat, or diagnose blood dyscrasia.

 Anemias are conditions in which the number of red blood cells or amount of hemoglobin (the protein that carries oxygen) in them is below normal. Anemia may be caused by excessive bleeding, decreased red blood cell production, or increased
10 red blood cell destruction (hemolysis). The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing anemias. Anemias that may be treated prevented or diagnosed by the polynucleotides, polypeptides, antibodies, and/or agonists or
15 antagonists of the present invention include iron deficiency anemia, hypochromic anemia, microcytic anemia, chlorosis, hereditary sideroblastic anemia, idiopathic acquired sideroblastic anemia, red cell aplasia, megaloblastic anemia (e.g., pernicious anemia, (vitamin B12 deficiency) and folic acid deficiency anemia), aplastic anemia, hemolytic anemias (e.g., autoimmune hemolytic anemia, microangiopathic hemolytic anemia, and paroxysmal nocturnal hemoglobinuria). The polynucleotides,
20 polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing anemias associated with diseases including but not limited to, anemias associated with systemic lupus erythematosus, cancers, lymphomas, chronic renal disease, and enlarged spleens. The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the
25 present invention may be useful in treating, preventing, and/or diagnosing anemias arising from drug treatments such as anemias associated with methyl dopa, dapsone, and/or sulfadriugs. Additionally, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing anemias associated with abnormal red blood cell architecture
30 including but not limited to, hereditary spherocytosis, hereditary elliptocytosis, glucose-6-phosphate dehydrogenase deficiency, and sickle cell anemia.

The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing hemoglobin abnormalities, (e.g., those associated with sickle cell anemia, hemoglobin C disease, hemoglobin S-C disease, and hemoglobin E disease). Additionally, the

5 polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating thalassemias, including, but not limited to major and minor forms of alpha-thalassemia and beta-thalassemia.

In another embodiment, the polynucleotides, polypeptides, antibodies, and/or

10 agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating bleeding disorders including, but not limited to, thrombocytopenia (e.g., idiopathic thrombocytopenic purpura, and thrombotic thrombocytopenic purpura), Von Willebrand's disease, hereditary platelet disorders (e.g., storage pool disease such as Chediak-Higashi and Hermansky-Pudlak

15 syndromes, thromboxane A2 dysfunction, thromboasthenia; and Bernard-Soulier syndrome), hemolytic-uremic syndrome, hemophelias such as hemophilia A or Factor VII deficiency and Christmas disease or Factor IX deficiency, Hereditary Hemorrhagic Telangiectasia, also known as Rendu-Osler-Weber syndrome, allergic purpura (Henoch Schonlein purpura) and disseminated intravascular coagulation.

20 The effect of the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention on the clotting time of blood may be monitored using any of the clotting tests known in the art including, but not limited to, whole blood partial thromboplastin time (PTT), the activated partial thromboplastin time (aPTT), the activated clotting time (ACT), the recalcified activated clotting time, or

25 the Lee-White Clotting time.

Several diseases and a variety of drugs can cause platelet dysfunction. Thus, in a specific embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating acquired platelet dysfunction such as platelet dysfunction

30 accompanying kidney failure, leukemia, multiple myeloma, cirrhosis of the liver, and systemic lupus erythematosus as well as platelet dysfunction associated with drug

treatments, including treatment with aspirin, ticlopidine, nonsteroidal anti-inflammatory drugs (used for arthritis, pain, and sprains), and penicillin in high doses.

In another embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing,

5 prognosing, preventing, and/or treating diseases and disorders characterized by or associated with increased or decreased numbers of white blood cells. Leukopenia occurs when the number of white blood cells decreases below normal. Leukopenias include, but are not limited to, neutropenia and lymphocytopenia. An increase in the number of white blood cells compared to normal is known as leukocytosis. The body
10 generates increased numbers of white blood cells during infection. Thus, leukocytosis may simply be a normal physiological parameter that reflects infection. Alternatively, leukocytosis may be an indicator of injury or other disease such as cancer.

Leukocytoses, include but are not limited to, eosinophilia, and accumulations of macrophages. In specific embodiments, the polynucleotides, polypeptides,

15 antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating leukopenia. In other specific embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating leukocytosis.

20 Leukopenia may be a generalized decreased in all types of white blood cells, or may be a specific depletion of particular types of white blood cells. Thus, in specific embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating decreases in neutrophil numbers, known as neutropenia.

25 Neutropenias that may be diagnosed, prognosed, prevented, and/or treated by the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention include, but are not limited to, infantile genetic agranulocytosis, familial neutropenia, cyclic neutropenia, neutropenias resulting from or associated with dietary deficiencies (e.g., vitamin B 12 deficiency or folic acid deficiency),

30 neutropenias resulting from or associated with drug treatments (e.g., antibiotic regimens such as penicillin treatment, sulfonamide treatment, anticoagulant treatment, anticonvulsant drugs, anti-thyroid drugs, and cancer chemotherapy), and neutropenias

resulting from increased neutrophil destruction that may occur in association with some bacterial or viral infections, allergic disorders, autoimmune diseases, conditions in which an individual has an enlarged spleen (e.g., Felty syndrome, malaria and sarcoidosis), and some drug treatment regimens.

- 5 The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating lymphocytopenias (decreased numbers of B and/or T lymphocytes), including, but not limited lymphocytopenias resulting from or associated with stress, drug treatments (e.g., drug treatment with corticosteroids, cancer chemotherapies, and/or radiation therapies), AIDS infection and/or other diseases such as, for example, cancer, rheumatoid arthritis, systemic lupus erythematosus, chronic infections, some viral infections and/or hereditary disorders (e.g., DiGeorge syndrome, Wiskott-Aldrich Syndrome, severe combined immunodeficiency, ataxia telangiectasia).

- 10 The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders associated with macrophage numbers and/or macrophage function including, but not limited to, Gaucher's disease, Niemann-Pick disease, Letterer-Siwe disease and Hand-Schuller-Christian disease.

- 15 In another embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders associated with eosinophil numbers and/or eosinophil function including, but not limited to, idiopathic hypereosinophilic syndrome, eosinophilia-myalgia syndrome, and Hand-Schuller-Christian disease.

- 20 In yet another embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating leukemias and lymphomas including, but not limited to, acute lymphocytic (lymphoblastic) leukemia (ALL), acute myeloid (myelocytic, myelogenous, myeloblastic, or myelomonocytic) leukemia, chronic lymphocytic leukemia (e.g., B cell leukemias, T cell leukemias, Sezary syndrome, and Hairy cell leukemia), chronic myelocytic (myeloid, myelogenous, or granulocytic)
- 25
- 30

leukemia, Hodgkin's lymphoma, non-hodgkin's lymphoma, Burkitt's lymphoma, and mycosis fungoides.

In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders of plasma cells including, but not limited to, plasma cell dyscrasias, monoclonal gammaopathies, monoclonal gammopathies of undetermined significance, multiple myeloma, macroglobulinemia, Waldenstrom's macroglobulinemia, cryoglobulinemia, and Raynaud's phenomenon.

10 In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing myeloproliferative disorders, including but not limited to, polycythemia vera, relative polycythemia, secondary polycythemia, myelofibrosis, acute myelofibrosis, agnogenic myelod metaplasia, thrombocythemia, (including both
15 primary and secondary thrombocythemia) and chronic myelocytic leukemia.

In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as a treatment prior to surgery, to increase blood cell production.

20 In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as an agent to enhance the migration, phagocytosis, superoxide production, antibody dependent cellular cytotoxicity of neutrophils, eosinophils and macrophages.

In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as an agent to increase
25 the number of stem cells in circulation prior to stem cells pheresis. In another specific embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as an agent to increase the number of stem cells in circulation prior to platelet pheresis.

30 In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as an agent to increase cytokine production.

In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in preventing, diagnosing, and/or treating primary hematopoietic disorders.

5 **Hyperproliferative Disorders**

In certain embodiments, polynucleotides or polypeptides, or agonists or antagonists of the present invention can be used to treat or detect hyperproliferative disorders, including neoplasms. Polynucleotides or polypeptides, or agonists or antagonists of the present invention may inhibit the proliferation of the disorder
10 through direct or indirect interactions. Alternatively, Polynucleotides or polypeptides, or agonists or antagonists of the present invention may proliferate other cells which can inhibit the hyperproliferative disorder.

For example, by increasing an immune response, particularly increasing antigenic qualities of the hyperproliferative disorder or by proliferating,
15 differentiating, or mobilizing T-cells, hyperproliferative disorders can be treated. This immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, decreasing an immune response may also be a method of treating hyperproliferative disorders, such as a chemotherapeutic agent.

20 Examples of hyperproliferative disorders that can be treated or detected by polynucleotides or polypeptides, or agonists or antagonists of the present invention include, but are not limited to neoplasms located in the: colon, abdomen, bone, breast, digestive system, liver, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous (central and
25 peripheral), lymphatic system, pelvis, skin, soft tissue, spleen, thorax, and urogenital tract.

Similarly, other hyperproliferative disorders can also be treated or detected by polynucleotides or polypeptides, or agonists or antagonists of the present invention. Examples of such hyperproliferative disorders include, but are not limited to: Acute
30 Childhood Lymphoblastic Leukemia, Acute Lymphoblastic Leukemia, Acute Lymphocytic Leukemia, Acute Myeloid Leukemia, Adrenocortical Carcinoma, Adult (Primary) Hepatocellular Cancer, Adult (Primary) Liver Cancer, Adult Acute

- Lymphocytic Leukemia, Adult Acute Myeloid Leukemia, Adult Hodgkin's Disease, Adult Hodgkin's Lymphoma, Adult Lymphocytic Leukemia, Adult Non-Hodgkin's Lymphoma, Adult Primary Liver Cancer, Adult Soft Tissue Sarcoma, AIDS-Related Lymphoma, AIDS-Related Malignancies, Anal Cancer, Astrocytoma, Bile Duct
- 5 Cancer, Bladder Cancer, Bone Cancer, Brain Stem Glioma, Brain Tumors, Breast Cancer, Cancer of the Renal Pelvis and Ureter, Central Nervous System (Primary) Lymphoma, Central Nervous System Lymphoma, Cerebellar Astrocytoma, Cerebral Astrocytoma, Cervical Cancer, Childhood (Primary) Hepatocellular Cancer, Childhood (Primary) Liver Cancer, Childhood Acute Lymphoblastic Leukemia,
- 10 Childhood Acute Myeloid Leukemia, Childhood Brain Stem Glioma, Childhood Cerebellar Astrocytoma, Childhood Cerebral Astrocytoma, Childhood Extracranial Germ Cell Tumors, Childhood Hodgkin's Disease, Childhood Hodgkin's Lymphoma, Childhood Hypothalamic and Visual Pathway Glioma, Childhood Lymphoblastic Leukemia, Childhood Medulloblastoma, Childhood Non-Hodgkin's Lymphoma,
- 15 Childhood Pineal and Supratentorial Primitive Neuroectodermal Tumors, Childhood Primary Liver Cancer, Childhood Rhabdomyosarcoma, Childhood Soft Tissue Sarcoma, Childhood Visual Pathway and Hypothalamic Glioma, Chronic Lymphocytic Leukemia, Chronic Myelogenous Leukemia, Colon Cancer, Cutaneous T-Cell Lymphoma, Endocrine Pancreas Islet Cell Carcinoma, Endometrial Cancer,
- 20 Ependymoma, Epithelial Cancer, Esophageal Cancer, Ewing's Sarcoma and Related Tumors, Exocrine Pancreatic Cancer, Extracranial Germ Cell Tumor, Extragonadal Germ Cell Tumor, Extrahepatic Bile Duct Cancer, Eye Cancer, Female Breast Cancer, Gaucher's Disease, Gallbladder Cancer, Gastric Cancer, Gastrointestinal Carcinoid Tumor, Gastrointestinal Tumors, Germ Cell Tumors, Gestational
- 25 Trophoblastic Tumor, Hairy Cell Leukemia, Head and Neck Cancer, Hepatocellular Cancer, Hodgkin's Disease, Hodgkin's Lymphoma, Hypergammaglobulinemia, Hypopharyngeal Cancer, Intestinal Cancers, Intraocular Melanoma, Islet Cell Carcinoma, Islet Cell Pancreatic Cancer, Kaposi's Sarcoma, Kidney Cancer, Laryngeal Cancer, Lip and Oral Cavity Cancer, Liver Cancer, Lung Cancer,
- 30 Lymphoproliferative Disorders, Macroglobulinemia, Male Breast Cancer, Malignant Mesothelioma, Malignant Thymoma, Medulloblastoma, Melanoma, Mesothelioma, Metastatic Occult Primary Squamous Neck Cancer, Metastatic Primary Squamous

Neck Cancer, Metastatic Squamous Neck Cancer, Multiple Myeloma, Multiple Myeloma/Plasma Cell Neoplasm, Myelodysplastic Syndrome, Myelogenous Leukemia, Myeloid Leukemia, Myeloproliferative Disorders, Nasal Cavity and Paranasal Sinus Cancer, Nasopharyngeal Cancer, Neuroblastoma, Non-Hodgkin's

5 Lymphoma During Pregnancy, Nonmelanoma Skin Cancer, Non-Small Cell Lung Cancer, Occult Primary Metastatic Squamous Neck Cancer, Oropharyngeal Cancer, Osteo-/Malignant Fibrous Sarcoma, Osteosarcoma/Malignant Fibrous Histiocytoma, Osteosarcoma/Malignant Fibrous Histiocytoma of Bone, Ovarian Epithelial Cancer, Ovarian Germ Cell Tumor, Ovarian Low Malignant Potential Tumor, Pancreatic

10 Cancer, Paraproteinemias, Purpura, Parathyroid Cancer, Penile Cancer, Pheochromocytoma, Pituitary Tumor, Plasma Cell Neoplasm/Multiple Myeloma, Primary Central Nervous System Lymphoma, Primary Liver Cancer, Prostate Cancer, Rectal Cancer, Renal Cell Cancer, Renal Pelvis and Ureter Cancer, Retinoblastoma, Rhabdomyosarcoma, Salivary Gland Cancer, Sarcoidosis Sarcomas, Sezary

15 Syndrome, Skin Cancer, Small Cell Lung Cancer, Small Intestine Cancer, Soft Tissue Sarcoma, Squamous Neck Cancer, Stomach Cancer, Supratentorial Primitive Neuroectodermal and Pineal Tumors, T-Cell Lymphoma, Testicular Cancer, Thymoma, Thyroid Cancer, Transitional Cell Cancer of the Renal Pelvis and Ureter, Transitional Renal Pelvis and Ureter Cancer, Trophoblastic Tumors, Ureter and Renal

20 Pelvis Cell Cancer, Urethral Cancer, Uterine Cancer, Uterine Sarcoma, Vaginal Cancer, Visual Pathway and Hypothalamic Glioma, Vulvar Cancer, Waldenstrom's Macroglobulinemia, Wilms' Tumor, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

In another preferred embodiment, polynucleotides or polypeptides, or agonists

25 or antagonists of the present invention are used to diagnose, prognose, prevent, and/or treat premalignant conditions and to prevent progression to a neoplastic or malignant state, including but not limited to those disorders described above. Such uses are indicated in conditions known or suspected of preceding progression to neoplasia or cancer, in particular, where non-neoplastic cell growth consisting of hyperplasia,

30 metaplasia, or most particularly, dysplasia has occurred (for review of such abnormal growth conditions, see Robbins and Angell, 1976, Basic Pathology, 2d Ed., W. B. Saunders Co., Philadelphia, pp. 68-79.)

Hyperplasia is a form of controlled cell proliferation, involving an increase in cell number in a tissue or organ, without significant alteration in structure or function. Hyperplastic disorders which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention (including polynucleotides, polypeptides, agonists or antagonists) include, but are not limited to, angiofollicular mediastinal lymph node hyperplasia, angiolymphoid hyperplasia with eosinophilia, atypical melanocytic hyperplasia, basal cell hyperplasia, benign giant lymph node hyperplasia, cementum hyperplasia, congenital adrenal hyperplasia, congenital sebaceous hyperplasia, cystic hyperplasia, cystic hyperplasia of the breast, denture hyperplasia, ductal hyperplasia, endometrial hyperplasia, fibromuscular hyperplasia, focal epithelial hyperplasia, gingival hyperplasia, inflammatory fibrous hyperplasia, inflammatory papillary hyperplasia, intravascular papillary endothelial hyperplasia, nodular hyperplasia of prostate, nodular regenerative hyperplasia, pseudoepitheliomatous hyperplasia, senile sebaceous hyperplasia, and verrucous hyperplasia.

Metaplasia is a form of controlled cell growth in which one type of adult or fully differentiated cell substitutes for another type of adult cell. Metaplastic disorders which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention (including polynucleotides, polypeptides, agonists or antagonists) include, but are not limited to, agnogenic myeloid metaplasia, apocrine metaplasia, atypical metaplasia, autoparenchymatous metaplasia, connective tissue metaplasia, epithelial metaplasia, intestinal metaplasia, metaplastic anemia, metaplastic ossification, metaplastic polyps, myeloid metaplasia, primary myeloid metaplasia, secondary myeloid metaplasia, squamous metaplasia, squamous metaplasia of amnion, and symptomatic myeloid metaplasia.

Dysplasia is frequently a forerunner of cancer, and is found mainly in the epithelia; it is the most disorderly form of non-neoplastic cell growth, involving a loss in individual cell uniformity and in the architectural orientation of cells. Dysplastic cells often have abnormally large, deeply stained nuclei, and exhibit pleomorphism. Dysplasia characteristically occurs where there exists chronic irritation or inflammation. Dysplastic disorders which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention (including polynucleotides, polypeptides, agonists or antagonists) include, but are not limited to, anhidrotic

ectodermal dysplasia, anterofacial dysplasia, asphyxiating thoracic dysplasia, atridigital dysplasia, bronchopulmonary dysplasia, cerebral dysplasia, cervical dysplasia, chondroectodermal dysplasia, cleidocranial dysplasia, congenital ectodermal dysplasia, craniodiaphysial dysplasia, craniocarpotarsal dysplasia, 5 craniometaphysial dysplasia, dentin dysplasia, diaphysial dysplasia, ectodermal dysplasia, enamel dysplasia, encephalo-ophthalmic dysplasia, dysplasia epiphysialis hemimelia, dysplasia epiphysialis multiplex, dysplasia epiphysialis punctata, epithelial dysplasia, faciodigitogenital dysplasia, familial fibrous dysplasia of jaws, familial white folded dysplasia, fibromuscular dysplasia, fibrous dysplasia of bone, 10 florid osseous dysplasia, hereditary renal-retinal dysplasia, hidrotic ectodermal dysplasia, hypohidrotic ectodermal dysplasia, lymphopenic thymic dysplasia, mammary dysplasia, mandibulofacial dysplasia, metaphysial dysplasia, Mondini dysplasia, monostotic fibrous dysplasia, mucoepithelial dysplasia, multiple epiphysial dysplasia, oculoauriculovertebral dysplasia, oculodentodigital dysplasia, 15 oculovertebral dysplasia, odontogenic dysplasia, ophthalmomandibulomelic dysplasia, periapical cemental dysplasia, polyostotic fibrous dysplasia, pseudoachondroplastic spondyloepiphysial dysplasia, retinal dysplasia, septo-optic dysplasia, spondyloepiphysial dysplasia, and ventriculoradial dysplasia.

Additional pre-neoplastic disorders which can be diagnosed, prognosed, 20 prevented, and/or treated with compositions of the invention (including polynucleotides, polypeptides, agonists or antagonists) include, but are not limited to, benign dysproliferative disorders (e.g., benign tumors, fibrocystic conditions, tissue hypertrophy, intestinal polyps, colon polyps, and esophageal dysplasia), leukoplakia, keratoses, Bowen's disease, Farmer's Skin, solar cheilitis, and solar keratosis.

25 In another embodiment, a polypeptide of the invention, or polynucleotides, antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to diagnose and/or prognose disorders associated with the tissue(s) in which the polypeptide of the invention is expressed, including one, two, three, four, five, or more tissues disclosed in Table 1B, column 8 (Tissue Distribution Library Code).

30 In another embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention conjugated to a toxin or a radioactive isotope, as described herein, may be used to treat cancers and neoplasms, including,

but not limited to those described herein. In a further preferred embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention conjugated to a toxin or a radioactive isotope, as described herein, may be used to treat acute myelogenous leukemia.

5 Additionally, polynucleotides, polypeptides, and/or agonists or antagonists of the invention may affect apoptosis, and therefore, would be useful in treating a number of diseases associated with increased cell survival or the inhibition of apoptosis. For example, diseases associated with increased cell survival or the inhibition of apoptosis that could be diagnosed, prognosed, prevented, and/or treated
10 by polynucleotides, polypeptides, and/or agonists or antagonists of the invention, include cancers (such as follicular lymphomas, carcinomas with p53 mutations, and hormone-dependent tumors, including, but not limited to colon cancer, cardiac tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma,
15 lymphoma, endothelioma, osteoblastoma, osteoclastoma, osteosarcoma, chondrosarcoma, adenoma, breast cancer, prostate cancer, Kaposi's sarcoma and ovarian cancer); autoimmune disorders such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related
20 glomerulonephritis and rheumatoid arthritis) and viral infections (such as herpes viruses, pox viruses and adenoviruses), inflammation, graft v. host disease, acute graft rejection, and chronic graft rejection.

 In preferred embodiments, polynucleotides, polypeptides, and/or agonists or antagonists of the invention are used to inhibit growth, progression, and/or metastasis
25 of cancers, in particular those listed above.

 Additional diseases or conditions associated with increased cell survival that could be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or agonists or antagonists of the invention, include, but are not limited to, progression, and/or metastases of malignancies and related disorders such
30 as leukemia (including acute leukemias (e.g., acute lymphocytic leukemia, acute myelocytic leukemia (including myeloblastic, promyelocytic, myelomonocytic, monocytic, and erythroleukemia)) and chronic leukemias (e.g., chronic myelocytic

(granulocytic) leukemia and chronic lymphocytic leukemia)), polycythemia vera, lymphomas (e.g., Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors including, but not limited to, sarcomas and carcinomas such as fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, emangioblastoma, acoustic neuroma, oligodendroglioma, menangioma, melanoma, neuroblastoma, and retinoblastoma.

Diseases associated with increased apoptosis that could be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or agonists or antagonists of the invention, include AIDS; neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, retinitis pigmentosa, cerebellar degeneration and brain tumor or prior associated disease); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) myelodysplastic syndromes (such as aplastic anemia), graft v. host disease, ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), liver injury (e.g., hepatitis related liver injury, ischemia/reperfusion injury, cholestasis (bile duct injury) and liver cancer); toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia.

Hyperproliferative diseases and/or disorders that could be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or agonists or antagonists of the invention, include, but are not limited to, neoplasms located in the liver, abdomen, bone, breast, digestive system, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous system (central and peripheral), lymphatic system, pelvis, skin, soft tissue, spleen, thorax, and urogenital tract.

Similarly, other hyperproliferative disorders can also be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or agonists or antagonists of the invention. Examples of such hyperproliferative disorders include, but are not limited to: hypergammaglobulinemia, lymphoproliferative disorders, paraproteinemias, purpura, sarcoidosis, Sezary Syndrome, Waldenstrom's macroglobulinemia, Gaucher's Disease, histiocytosis, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

Another preferred embodiment utilizes polynucleotides of the present invention to inhibit aberrant cellular division, by gene therapy using the present invention, and/or protein fusions or fragments thereof.

Thus, the present invention provides a method for treating cell proliferative disorders by inserting into an abnormally proliferating cell a polynucleotide of the present invention, wherein said polynucleotide represses said expression.

Another embodiment of the present invention provides a method of treating cell-proliferative disorders in individuals comprising administration of one or more active gene copies of the present invention to an abnormally proliferating cell or cells. In a preferred embodiment, polynucleotides of the present invention is a DNA construct comprising a recombinant expression vector effective in expressing a DNA sequence encoding said polynucleotides. In another preferred embodiment of the present invention, the DNA construct encoding the polynucleotides of the present invention is inserted into cells to be treated utilizing a retrovirus, or more preferably an adenoviral vector (See G J. Nabel, et. al., PNAS 1999 96: 324-326, which is hereby incorporated by reference). In a most preferred embodiment, the viral vector is defective and will not transform non-proliferating cells, only proliferating cells. Moreover, in a preferred embodiment, the polynucleotides of the present invention

inserted into proliferating cells either alone, or in combination with or fused to other polynucleotides, can then be modulated via an external stimulus (i.e. magnetic, specific small molecule, chemical, or drug administration, etc.), which acts upon the promoter upstream of said polynucleotides to induce expression of the encoded protein product. As such the beneficial therapeutic affect of the present invention may be expressly modulated (i.e. to increase, decrease, or inhibit expression of the present invention) based upon said external stimulus.

Polynucleotides of the present invention may be useful in repressing expression of oncogenic genes or antigens. By "repressing expression of the oncogenic genes " is intended the suppression of the transcription of the gene, the degradation of the gene transcript (pre-message RNA), the inhibition of splicing, the destruction of the messenger RNA, the prevention of the post-translational modifications of the protein, the destruction of the protein, or the inhibition of the normal function of the protein.

For local administration to abnormally proliferating cells, polynucleotides of the present invention may be administered by any method known to those of skill in the art including, but not limited to transfection, electroporation, microinjection of cells, or in vehicles such as liposomes, lipofectin, or as naked polynucleotides, or any other method described throughout the specification. The polynucleotide of the present invention may be delivered by known gene delivery systems such as, but not limited to, retroviral vectors (Gilboa, J. Virology 44:845 (1982); Hocke, Nature 320:275 (1986); Wilson, et al., Proc. Natl. Acad. Sci. U.S.A. 85:3014), vaccinia virus system (Chakrabarty et al., Mol. Cell Biol. 5:3403 (1985) or other efficient DNA delivery systems (Yates et al., Nature 313:812 (1985)) known to those skilled in the art. These references are exemplary only and are hereby incorporated by reference. In order to specifically deliver or transfect cells which are abnormally proliferating and spare non-dividing cells, it is preferable to utilize a retrovirus, or adenoviral (as described in the art and elsewhere herein) delivery system known to those of skill in the art. Since host DNA replication is required for retroviral DNA to integrate and the retrovirus will be unable to self replicate due to the lack of the retrovirus genes needed for its life cycle. Utilizing such a retroviral delivery system for

polynucleotides of the present invention will target said gene and constructs to abnormally proliferating cells and will spare the non-dividing normal cells.

The polynucleotides of the present invention may be delivered directly to cell-proliferative disorder/disease sites in internal organs, body cavities and the like by use of imaging devices used to guide an injecting needle directly to the disease site. The polynucleotides of the present invention may also be administered to disease sites at the time of surgical intervention.

By "cell proliferative disease" is meant any human or animal disease or disorder, affecting any one or any combination of organs, cavities, or body parts, which is characterized by single or multiple local abnormal proliferations of cells, groups of cells, or tissues, whether benign or malignant.

Any amount of the polynucleotides of the present invention may be administered as long as it has a biologically inhibiting effect on the proliferation of the treated cells. Moreover, it is possible to administer more than one of the polynucleotide of the present invention simultaneously to the same site. By "biologically inhibiting" is meant partial or total growth inhibition as well as decreases in the rate of proliferation or growth of the cells. The biologically inhibitory dose may be determined by assessing the effects of the polynucleotides of the present invention on target malignant or abnormally proliferating cell growth in tissue culture, tumor growth in animals and cell cultures, or any other method known to one of ordinary skill in the art.

The present invention is further directed to antibody-based therapies which involve administering of anti-polypeptides and anti-polynucleotide antibodies to a mammalian, preferably human, patient for treating one or more of the described disorders. Methods for producing anti-polypeptides and anti-polynucleotide antibodies polyclonal and monoclonal antibodies are described in detail elsewhere herein. Such antibodies may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

A summary of the ways in which the antibodies of the present invention may be used therapeutically includes binding polynucleotides or polypeptides of the present invention locally or systemically in the body or by direct cytotoxicity of the antibody, e.g. as mediated by complement (CDC) or by effector cells (ADCC). Some

of these approaches are described in more detail below. Armed with the teachings provided herein, one of ordinary skill in the art will know how to use the antibodies of the present invention for diagnostic, monitoring or therapeutic purposes without undue experimentation.

5 In particular, the antibodies, fragments and derivatives of the present invention are useful for treating a subject having or developing cell proliferative and/or differentiation disorders as described herein. Such treatment comprises administering a single or multiple doses of the antibody, or a fragment, derivative, or a conjugate thereof.

10 The antibodies of this invention may be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth factors, for example., which serve to increase the number or activity of effector cells which interact with the antibodies.

It is preferred to use high affinity and/or potent *in vivo* inhibiting and/or
15 neutralizing antibodies against polypeptides or polynucleotides of the present invention, fragments or regions thereof, for both immunoassays directed to and therapy of disorders related to polynucleotides or polypeptides, including fragments thereof, of the present invention. Such antibodies, fragments, or regions, will preferably have an affinity for polynucleotides or polypeptides, including fragments
20 thereof. Preferred binding affinities include those with a dissociation constant or K_d less than $5 \times 10^{-6}M$, $10^{-6}M$, $5 \times 10^{-7}M$, $10^{-7}M$, $5 \times 10^{-8}M$, $10^{-8}M$, $5 \times 10^{-9}M$, $10^{-9}M$, $5 \times 10^{-10}M$, $10^{-10}M$, $5 \times 10^{-11}M$, $10^{-11}M$, $5 \times 10^{-12}M$, $10^{-12}M$, $5 \times 10^{-13}M$, $10^{-13}M$, $5 \times 10^{-14}M$, $10^{-14}M$, $5 \times 10^{-15}M$, and $10^{-15}M$.

Moreover, polypeptides of the present invention are useful in inhibiting the
25 angiogenesis of proliferative cells or tissues, either alone, as a protein fusion, or in combination with other polypeptides directly or indirectly, as described elsewhere herein. In a most preferred embodiment, said anti-angiogenesis effect may be achieved indirectly, for example, through the inhibition of hematopoietic, tumor-specific cells, such as tumor-associated macrophages (See Joseph IB, et al. J Natl
30 Cancer Inst, 90(21):1648-53 (1998), which is hereby incorporated by reference). Antibodies directed to polypeptides or polynucleotides of the present invention may also result in inhibition of angiogenesis directly, or indirectly (See Witte L, et al.,

Cancer Metastasis Rev. 17(2):155-61 (1998), which is hereby incorporated by reference)).

Polypeptides, including protein fusions, of the present invention, or fragments thereof may be useful in inhibiting proliferative cells or tissues through the induction of apoptosis. Said polypeptides may act either directly, or indirectly to induce apoptosis of proliferative cells and tissues, for example in the activation of a death-domain receptor, such as tumor necrosis factor (TNF) receptor-1, CD95 (Fas/APO-1), TNF-receptor-related apoptosis-mediated protein (TRAMP) and TNF-related apoptosis-inducing ligand (TRAIL) receptor-1 and -2 (See Schulze-Osthoff K, et.al., Eur J Biochem 254(3):439-59 (1998), which is hereby incorporated by reference). Moreover, in another preferred embodiment of the present invention, said polypeptides may induce apoptosis through other mechanisms, such as in the activation of other proteins which will activate apoptosis, or through stimulating the expression of said proteins, either alone or in combination with small molecule drugs or adjuvants, such as apoptonin, galectins, thioredoxins, anti-inflammatory proteins (See for example, Mutat Res 400(1-2):447-55 (1998), Med Hypotheses.50(5):423-33 (1998), Chem Biol Interact. Apr 24;111-112:23-34 (1998), J Mol Med.76(6):402-12 (1998), Int J Tissue React;20(1):3-15 (1998), which are all hereby incorporated by reference).

Polypeptides, including protein fusions to, or fragments thereof, of the present invention are useful in inhibiting the metastasis of proliferative cells or tissues. Inhibition may occur as a direct result of administering polypeptides, or antibodies directed to said polypeptides as described elsewhere herein, or indirectly, such as activating the expression of proteins known to inhibit metastasis, for example alpha 4 integrins, (See, e.g., Curr Top Microbiol Immunol 1998;231:125-41, which is hereby incorporated by reference). Such therapeutic affects of the present invention may be achieved either alone, or in combination with small molecule drugs or adjuvants.

In another embodiment, the invention provides a method of delivering compositions containing the polypeptides of the invention (e.g., compositions containing polypeptides or polypeptide antibodies associated with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs) to targeted cells expressing the polypeptide of the present invention. Polypeptides or polypeptide

antibodies of the invention may be associated with with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs via hydrophobic, hydrophilic, ionic and/or covalent interactions.

Polypeptides, protein fusions to, or fragments thereof, of the present invention are useful in enhancing the immunogenicity and/or antigenicity of proliferating cells or tissues, either directly, such as would occur if the polypeptides of the present invention 'vaccinated' the immune response to respond to proliferative antigens and immunogens, or indirectly, such as in activating the expression of proteins known to enhance the immune response (e.g. chemokines), to said antigens and immunogens.

Renal Disorders

Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention, may be used to treat, prevent, diagnose, and/or prognose disorders of the renal system. Renal disorders which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention include, but are not limited to, kidney failure, nephritis, blood vessel disorders of kidney, metabolic and congenital kidney disorders, urinary disorders of the kidney, autoimmune disorders, sclerosis and necrosis, electrolyte imbalance, and kidney cancers.

Kidney diseases which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention include, but are not limited to, acute kidney failure, chronic kidney failure, atheroembolic renal failure, end-stage renal disease, inflammatory diseases of the kidney (e.g., acute glomerulonephritis, postinfectious glomerulonephritis, rapidly progressive glomerulonephritis, nephrotic syndrome, membranous glomerulonephritis, familial nephrotic syndrome, membranoproliferative glomerulonephritis I and II, mesangial proliferative glomerulonephritis, chronic glomerulonephritis, acute tubulointerstitial nephritis, chronic tubulointerstitial nephritis, acute post-streptococcal glomerulonephritis (PSGN), pyelonephritis, lupus nephritis, chronic nephritis, interstitial nephritis, and post-streptococcal glomerulonephritis), blood vessel disorders of the kidneys (e.g., kidney infarction, atheroembolic kidney disease, cortical necrosis, malignant nephrosclerosis, renal vein thrombosis, renal underperfusion, renal retinopathy, renal ischemia-reperfusion, renal

artery embolism, and renal artery stenosis), and kidney disorders resulting from urinary tract disease (e.g., pyelonephritis, hydronephrosis, urolithiasis (renal lithiasis, nephrolithiasis), reflux nephropathy, urinary tract infections, urinary retention, and acute or chronic unilateral obstructive uropathy.)

- 5 In addition, compositions of the invention can be used to diagnose, prognose, prevent, and/or treat metabolic and congenital disorders of the kidney (e.g., uremia, renal amyloidosis, renal osteodystrophy, renal tubular acidosis, renal glycosuria, nephrogenic diabetes insipidus, cystinuria, Fanconi's syndrome, renal fibrocystic osteosis (renal rickets), Hartnup disease, Bartter's syndrome, Liddle's syndrome, 10 polycystic kidney disease, medullary cystic disease, medullary sponge kidney, Alport's syndrome, nail-patella syndrome, congenital nephrotic syndrome, CRUSH syndrome, horseshoe kidney, diabetic nephropathy, nephrogenic diabetes insipidus, analgesic nephropathy, kidney stones, and membranous nephropathy), and autoimmune disorders of the kidney (e.g., systemic lupus erythematosus (SLE), 15 Goodpasture syndrome, IgA nephropathy, and IgM mesangial proliferative glomerulonephritis).

- Compositions of the invention can also be used to diagnose, prognose, prevent, and/or treat sclerotic or necrotic disorders of the kidney (e.g., glomerulosclerosis, diabetic nephropathy, focal segmental glomerulosclerosis 20 (FSGS), necrotizing glomerulonephritis, and renal papillary necrosis), cancers of the kidney (e.g., nephroma, hypernephroma, nephroblastoma, renal cell cancer, transitional cell cancer, renal adenocarcinoma, squamous cell cancer, and Wilm's tumor), and electrolyte imbalances (e.g., nephrocalcinosis, pyuria, edema, hydronephritis, proteinuria, hyponatremia, hypernatremia, hypokalemia, 25 hyperkalemia, hypocalcemia, hypercalcemia, hypophosphatemia, and hyperphosphatemia).

- Polypeptides may be administered using any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, biolistic injectors, particle 30 accelerators, gelfoam sponge depots, other commercially available depot materials, osmotic pumps, oral or suppository solid pharmaceutical formulations, decanting or topical applications during surgery, aerosol delivery. Such methods are known in the

art. Polypeptides may be administered as part of a Therapeutic, described in more detail below. Methods of delivering polynucleotides are described in more detail herein.

5 **Cardiovascular Disorders**

Polynucleotides or polypeptides, or agonists or antagonists of the present invention, may be used to treat, prevent, diagnose, and/or prognose cardiovascular disorders, including, but not limited to, peripheral artery disease, such as limb ischemia.

10 Cardiovascular disorders include, but are not limited to, cardiovascular abnormalities, such as arterio-arterial fistula, arteriovenous fistula, cerebral arteriovenous malformations, congenital heart defects, pulmonary atresia, and Scimitar Syndrome. Congenital heart defects include, but are not limited to, aortic coarctation, cor triatriatum, coronary vessel anomalies, crisscross heart, dextrocardia,
 15 patent ductus arteriosus, Ebstein's anomaly, Eisenmenger complex, hypoplastic left heart syndrome, levocardia, tetralogy of fallot, transposition of great vessels, double outlet right ventricle, tricuspid atresia, persistent truncus arteriosus, and heart septal defects, such as aortopulmonary septal defect, endocardial cushion defects, Lutembacher's Syndrome, trilog of Fallot, ventricular heart septal defects.

20 Cardiovascular disorders also include, but are not limited to, heart disease, such as arrhythmias, carcinoid heart disease, high cardiac output, low cardiac output, cardiac tamponade, endocarditis (including bacterial), heart aneurysm, cardiac arrest, congestive heart failure, congestive cardiomyopathy, paroxysmal dyspnea, cardiac edema, heart hypertrophy, congestive cardiomyopathy, left ventricular hypertrophy,
 25 right ventricular hypertrophy, post-infarction heart rupture, ventricular septal rupture, heart valve diseases, myocardial diseases, myocardial ischemia, pericardial effusion, pericarditis (including constrictive and tuberculous), pneumopericardium, postpericardiotomy syndrome, pulmonary heart disease, rheumatic heart disease, ventricular dysfunction, hyperemia, cardiovascular pregnancy complications, Scimitar
 30 Syndrome, cardiovascular syphilis, and cardiovascular tuberculosis.

Arrhythmias include, but are not limited to, sinus arrhythmia, atrial fibrillation, atrial flutter, bradycardia, extrasystole, Adams-Stokes Syndrome, bundle-

branch block, sinoatrial block, long QT syndrome, parasystole, Lown-Ganong-Levine Syndrome, Mahaim-type pre-excitation syndrome, Wolff-Parkinson-White syndrome, sick sinus syndrome, tachycardias, and ventricular fibrillation. Tachycardias include paroxysmal tachycardia, supraventricular tachycardia, accelerated idioventricular
5 rhythm, atrioventricular nodal reentry tachycardia, ectopic atrial tachycardia, ectopic junctional tachycardia, sinoatrial nodal reentry tachycardia, sinus tachycardia, Torsades de Pointes, and ventricular tachycardia.

Heart valve diseases include, but are not limited to, aortic valve insufficiency, aortic valve stenosis, hear murmurs, aortic valve prolapse, mitral valve prolapse,
10 tricuspid valve prolapse, mitral valve insufficiency, mitral valve stenosis, pulmonary atresia, pulmonary valve insufficiency, pulmonary valve stenosis, tricuspid atresia, tricuspid valve insufficiency, and tricuspid valve stenosis.

Myocardial diseases include, but are not limited to, alcoholic cardiomyopathy, congestive cardiomyopathy, hypertrophic cardiomyopathy, aortic subvalvular
15 stenosis, pulmonary subvalvular stenosis, restrictive cardiomyopathy, Chagas cardiomyopathy, endocardial fibroelastosis, endomyocardial fibrosis, Kearns Syndrome, myocardial reperfusion injury, and myocarditis.

Myocardial ischemias include, but are not limited to, coronary disease, such as angina pectoris, coronary aneurysm, coronary arteriosclerosis, coronary thrombosis,
20 coronary vasospasm, myocardial infarction and myocardial stunning.

Cardiovascular diseases also include vascular diseases such as aneurysms, angiodyplasia, angiomatosis, bacillary angiomatosis, Hippel-Lindau Disease, Klippel-Trenaunay-Weber Syndrome, Sturge-Weber Syndrome, angioneurotic edema, aortic diseases, Takayasu's Arteritis, aortitis, Leriche's Syndrome, arterial occlusive
25 diseases, arteritis, enarteritis, polyarteritis nodosa, cerebrovascular disorders, diabetic angiopathies, diabetic retinopathy, embolisms, thrombosis, erythromelalgia, hemorrhoids, hepatic veno-occlusive disease, hypertension, hypotension, ischemia, peripheral vascular diseases, phlebitis, pulmonary veno-occlusive disease, Raynaud's disease, CREST syndrome, retinal vein occlusion, Scimitar syndrome, superior vena
30 cava syndrome, telangiectasia, atacia telangiectasia, hereditary hemorrhagic telangiectasia, varicocele, varicose veins, varicose ulcer, vasculitis, and venous insufficiency.

Aneurysms include, but are not limited to, dissecting aneurysms, false aneurysms, infected aneurysms, ruptured aneurysms, aortic aneurysms, cerebral aneurysms, coronary aneurysms, heart aneurysms, and iliac aneurysms.

Arterial occlusive diseases include, but are not limited to, arteriosclerosis, intermittent claudication, carotid stenosis, fibromuscular dysplasias, mesenteric vascular occlusion, Moyamoya disease, renal artery obstruction, retinal artery occlusion, and thromboangiitis obliterans.

Cerebrovascular disorders include, but are not limited to, carotid artery diseases, cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformation, cerebral artery diseases, cerebral embolism and thrombosis, carotid artery thrombosis, sinus thrombosis, Wallenberg's syndrome, cerebral hemorrhage, epidural hematoma, subdural hematoma, subarachnoid hemorrhage, cerebral infarction, cerebral ischemia (including transient), subclavian steal syndrome, periventricular leukomalacia, vascular headache, cluster headache, migraine, and vertebrobasilar insufficiency.

Embolisms include, but are not limited to, air embolisms, amniotic fluid embolisms, cholesterol embolisms, blue toe syndrome, fat embolisms, pulmonary embolisms, and thromboembolisms. Thrombosis include, but are not limited to, coronary thrombosis, hepatic vein thrombosis, retinal vein occlusion, carotid artery thrombosis, sinus thrombosis, Wallenberg's syndrome, and thrombophlebitis.

Ischemic disorders include, but are not limited to, cerebral ischemia, ischemic colitis, compartment syndromes, anterior compartment syndrome, myocardial ischemia, reperfusion injuries, and peripheral limb ischemia. Vasculitis includes, but is not limited to, aortitis, arteritis, Behcet's Syndrome, Churg-Strauss Syndrome, mucocutaneous lymph node syndrome, thromboangiitis obliterans, hypersensitivity vasculitis, Schoenlein-Henoch purpura, allergic cutaneous vasculitis, and Wegener's granulomatosis.

Polypeptides may be administered using any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, biolistic injectors, particle accelerators, gelfoam sponge depots, other commercially available depot materials, osmotic pumps, oral or suppository solid pharmaceutical formulations, decanting or

topical applications during surgery, aerosol delivery. Such methods are known in the art. Polypeptides may be administered as part of a Therapeutic, described in more detail below. Methods of delivering polynucleotides are described in more detail herein.

5

Respiratory Disorders

Polynucleotides or polypeptides, or agonists or antagonists of the present invention may be used to treat, prevent, diagnose, and/or prognose diseases and/or disorders of the respiratory system.

10 Diseases and disorders of the respiratory system include, but are not limited to, nasal vestibulitis, nonallergic rhinitis (e.g., acute rhinitis, chronic rhinitis, atrophic rhinitis, vasomotor rhinitis), nasal polyps, and sinusitis, juvenile angiofibromas, cancer of the nose and juvenile papillomas, vocal cord polyps, nodules (singer's nodules), contact ulcers, vocal cord paralysis, laryngoceles, pharyngitis (e.g., viral and
15 bacterial), tonsillitis, tonsillar cellulitis, parapharyngeal abscess, laryngitis, laryngoceles, and throat cancers (e.g., cancer of the nasopharynx, tonsil cancer, larynx cancer), lung cancer (e.g., squamous cell carcinoma, small cell (oat cell) carcinoma, large cell carcinoma, and adenocarcinoma), allergic disorders (eosinophilic pneumonia, hypersensitivity pneumonitis (e.g., extrinsic allergic alveolitis, allergic
20 interstitial pneumonitis, organic dust pneumoconiosis, allergic bronchopulmonary aspergillosis, asthma, Wegener's granulomatosis (granulomatous vasculitis), Goodpasture's syndrome)), pneumonia (e.g., bacterial pneumonia (e.g., *Streptococcus pneumoniae* (pneumococcal pneumonia), *Staphylococcus aureus* (staphylococcal pneumonia), Gram-negative bacterial pneumonia (caused by, e.g., *Klebsiella* and
25 *Pseudomonas spp.*), *Mycoplasma pneumoniae* pneumonia, *Hemophilus influenzae* pneumonia, *Legionella pneumophila* (Legionnaires' disease), and *Chlamydia psittaci* (Psittacosis)), and viral pneumonia (e.g., influenza, chickenpox (varicella).

Additional diseases and disorders of the respiratory system include, but are not limited to bronchiolitis, polio (poliomyelitis), croup, respiratory syncytial viral
30 infection, mumps, erythema infectiosum (fifth disease), roseola infantum, progressive rubella panencephalitis, german measles, and subacute sclerosing panencephalitis, fungal pneumonia (e.g., Histoplasmosis, Coccidioidomycosis, Blastomycosis, fungal

infections in people with severely suppressed immune systems (e.g., cryptococcosis, caused by *Cryptococcus neoformans*; aspergillosis, caused by *Aspergillus spp.*; candidiasis, caused by *Candida*; and mucormycosis)), *Pneumocystis carinii* (pneumocystis pneumonia), atypical pneumonias (e.g., *Mycoplasma* and *Chlamydia* spp.), opportunistic infection pneumonia, nosocomial pneumonia, chemical pneumonitis, and aspiration pneumonia, pleural disorders (e.g., pleurisy, pleural effusion, and pneumothorax (e.g., simple spontaneous pneumothorax, complicated spontaneous pneumothorax, tension pneumothorax)), obstructive airway diseases (e.g., asthma, chronic obstructive pulmonary disease (COPD), emphysema, chronic or acute bronchitis), occupational lung diseases (e.g., silicosis, black lung (coal workers' pneumoconiosis), asbestosis, berylliosis, occupational asthma, byssinosis, and benign pneumoconioses), Infiltrative Lung Disease (e.g., pulmonary fibrosis (e.g., fibrosing alveolitis, usual interstitial pneumonia), idiopathic pulmonary fibrosis, desquamative interstitial pneumonia, lymphoid interstitial pneumonia, histiocytosis X (e.g., Letterer-Siwe disease, Hand-Schüller-Christian disease, eosinophilic granuloma), idiopathic pulmonary hemosiderosis, sarcoidosis and pulmonary alveolar proteinosis), Acute respiratory distress syndrome (also called, e.g., adult respiratory distress syndrome), edema, pulmonary embolism, bronchitis (e.g., viral, bacterial), bronchiectasis, atelectasis, lung abscess (caused by, e.g., *Staphylococcus aureus* or *Legionella pneumophila*), and cystic fibrosis.

Anti-Angiogenesis Activity

The naturally occurring balance between endogenous stimulators and inhibitors of angiogenesis is one in which inhibitory influences predominate. Rastinejad *et al.*, *Cell* 56:345-355 (1989). In those rare instances in which neovascularization occurs under normal physiological conditions, such as wound healing, organ regeneration, embryonic development, and female reproductive processes, angiogenesis is stringently regulated and spatially and temporally delimited. Under conditions of pathological angiogenesis such as that characterizing solid tumor growth, these regulatory controls fail. Unregulated angiogenesis becomes pathologic and sustains progression of many neoplastic and non-neoplastic diseases. A number of serious diseases are dominated by abnormal neovascularization

including solid tumor growth and metastases, arthritis, some types of eye disorders, and psoriasis. See, e.g., reviews by Moses *et al.*, *Biotech.* 9:630-634 (1991); Folkman *et al.*, *N. Engl. J. Med.*, 333:1757-1763 (1995); Auerbach *et al.*, *J. Microvasc. Res.* 29:401-411 (1985); Folkman, *Advances in Cancer Research*, eds. Klein and Weinhouse, Academic Press, New York, pp. 175-203 (1985); Patz, *Am. J. Ophthalmol.* 94:715-743 (1982); and Folkman *et al.*, *Science* 221:719-725 (1983). In a number of pathological conditions, the process of angiogenesis contributes to the disease state. For example, significant data have accumulated which suggest that the growth of solid tumors is dependent on angiogenesis. Folkman and Klagsbrun, *Science* 235:442-447 (1987).

The present invention provides for treatment of diseases or disorders associated with neovascularization by administration of the polynucleotides and/or polypeptides of the invention, as well as agonists or antagonists of the present invention. Malignant and metastatic conditions which can be treated with the polynucleotides and polypeptides, or agonists or antagonists of the invention include, but are not limited to, malignancies, solid tumors, and cancers described herein and otherwise known in the art (for a review of such disorders, see Fishman *et al.*, *Medicine*, 2d Ed., J. B. Lippincott Co., Philadelphia (1985)). Thus, the present invention provides a method of treating an angiogenesis-related disease and/or disorder, comprising administering to an individual in need thereof a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist of the invention. For example, polynucleotides, polypeptides, antagonists and/or agonists may be utilized in a variety of additional methods in order to therapeutically treat a cancer or tumor. Cancers which may be treated with polynucleotides, polypeptides, antagonists and/or agonists include, but are not limited to solid tumors, including prostate, lung, breast, ovarian, stomach, pancreas, larynx, esophagus, testes, liver, parotid, biliary tract, colon, rectum, cervix, uterus, endometrium, kidney, bladder, thyroid cancer; primary tumors and metastases; melanomas; glioblastoma; Kaposi's sarcoma; leiomyosarcoma; non-small cell lung cancer; colorectal cancer; advanced malignancies; and blood born tumors such as leukemias. For example, polynucleotides, polypeptides, antagonists and/or agonists may be delivered topically, in order to treat cancers such as skin cancer, head and neck tumors, breast tumors, and

Kaposi's sarcoma.

Within yet other aspects, polynucleotides, polypeptides, antagonists and/or agonists may be utilized to treat superficial forms of bladder cancer by, for example, intravesical administration. Polynucleotides, polypeptides, antagonists and/or agonists
5 may be delivered directly into the tumor, or near the tumor site, via injection or a catheter. Of course, as the artisan of ordinary skill will appreciate, the appropriate mode of administration will vary according to the cancer to be treated. Other modes of delivery are discussed herein.

Polynucleotides, polypeptides, antagonists and/or agonists may be useful in
10 treating other disorders, besides cancers, which involve angiogenesis. These disorders include, but are not limited to: benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas; arteriosclerotic plaques; ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular
15 glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, uveitis and Pterygia (abnormal blood vessel growth) of the eye; rheumatoid arthritis; psoriasis; delayed wound healing; endometriosis; vasculogenesis; granulations; hypertrophic scars (keloids); nonunion fractures; scleroderma; trachoma; vascular adhesions; myocardial angiogenesis; coronary collaterals; cerebral collaterals; arteriovenous malformations;
20 ischemic limb angiogenesis; Osler-Webber Syndrome; plaque neovascularization; telangiectasia; hemophilic joints; angiofibroma; fibromuscular dysplasia; wound granulation; Crohn's disease; and atherosclerosis.

For example, within one aspect of the present invention methods are provided for treating hypertrophic scars and keloids, comprising the step of administering a
25 polynucleotide, polypeptide, antagonist and/or agonist of the invention to a hypertrophic scar or keloid.

Within one embodiment of the present invention polynucleotides, polypeptides, antagonists and/or agonists of the invention are directly injected into a hypertrophic scar or keloid, in order to prevent the progression of these lesions. This
30 therapy is of particular value in the prophylactic treatment of conditions which are known to result in the development of hypertrophic scars and keloids (e.g., burns), and is preferably initiated after the proliferative phase has had time to progress

(approximately 14 days after the initial injury), but before hypertrophic scar or keloid development. As noted above, the present invention also provides methods for treating neovascular diseases of the eye, including for example, corneal neovascularization, neovascular glaucoma, proliferative diabetic retinopathy, retrolental fibroplasia and macular degeneration.

Moreover, Ocular disorders associated with neovascularization which can be treated with the polynucleotides and polypeptides of the present invention (including agonists and/or antagonists) include, but are not limited to: neovascular glaucoma, diabetic retinopathy, retinoblastoma, retrolental fibroplasia, uveitis, retinopathy of prematurity macular degeneration, corneal graft neovascularization, as well as other eye inflammatory diseases, ocular tumors and diseases associated with choroidal or iris neovascularization. See, e.g., reviews by Waltman *et al.*, *Am. J. Ophthalmol.* 85:704-710 (1978) and Gartner *et al.*, *Surv. Ophthalmol.* 22:291-312 (1978).

Thus, within one aspect of the present invention methods are provided for treating neovascular diseases of the eye such as corneal neovascularization (including corneal graft neovascularization), comprising the step of administering to a patient a therapeutically effective amount of a compound (as described above) to the cornea, such that the formation of blood vessels is inhibited. Briefly, the cornea is a tissue which normally lacks blood vessels. In certain pathological conditions however, capillaries may extend into the cornea from the pericorneal vascular plexus of the limbus. When the cornea becomes vascularized, it also becomes clouded, resulting in a decline in the patient's visual acuity. Visual loss may become complete if the cornea completely opacitates. A wide variety of disorders can result in corneal neovascularization, including for example, corneal infections (e.g., trachoma, herpes simplex keratitis, leishmaniasis and onchocerciasis), immunological processes (e.g., graft rejection and Stevens-Johnson's syndrome), alkali burns, trauma, inflammation (of any cause), toxic and nutritional deficiency states, and as a complication of wearing contact lenses.

Within particularly preferred embodiments of the invention, may be prepared for topical administration in saline (combined with any of the preservatives and antimicrobial agents commonly used in ocular preparations), and administered in eyedrop form. The solution or suspension may be prepared in its pure form and

administered several times daily. Alternatively, anti-angiogenic compositions, prepared as described above, may also be administered directly to the cornea. Within preferred embodiments, the anti-angiogenic composition is prepared with a muco-adhesive polymer which binds to cornea. Within further embodiments, the anti-angiogenic factors or anti-angiogenic compositions may be utilized as an adjunct to conventional steroid therapy. Topical therapy may also be useful prophylactically in corneal lesions which are known to have a high probability of inducing an angiogenic response (such as chemical burns). In these instances the treatment, likely in combination with steroids, may be instituted immediately to help prevent subsequent complications.

Within other embodiments, the compounds described above may be injected directly into the corneal stroma by an ophthalmologist under microscopic guidance. The preferred site of injection may vary with the morphology of the individual lesion, but the goal of the administration would be to place the composition at the advancing front of the vasculature (i.e., interspersed between the blood vessels and the normal cornea). In most cases this would involve perilimbic corneal injection to "protect" the cornea from the advancing blood vessels. This method may also be utilized shortly after a corneal insult in order to prophylactically prevent corneal neovascularization. In this situation the material could be injected in the perilimbic cornea interspersed between the corneal lesion and its undesired potential limbic blood supply. Such methods may also be utilized in a similar fashion to prevent capillary invasion of transplanted corneas. In a sustained-release form injections might only be required 2-3 times per year. A steroid could also be added to the injection solution to reduce inflammation resulting from the injection itself.

Within another aspect of the present invention, methods are provided for treating neovascular glaucoma, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist to the eye, such that the formation of blood vessels is inhibited. In one embodiment, the compound may be administered topically to the eye in order to treat early forms of neovascular glaucoma. Within other embodiments, the compound may be implanted by injection into the region of the anterior chamber angle. Within other embodiments, the compound may also be placed in any location such that the

compound is continuously released into the aqueous humor. Within another aspect of the present invention, methods are provided for treating proliferative diabetic retinopathy, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist to the eyes, such that the formation of blood vessels is inhibited.

Within particularly preferred embodiments of the invention, proliferative diabetic retinopathy may be treated by injection into the aqueous humor or the vitreous, in order to increase the local concentration of the polynucleotide, polypeptide, antagonist and/or agonist in the retina. Preferably, this treatment should be initiated prior to the acquisition of severe disease requiring photocoagulation.

Within another aspect of the present invention, methods are provided for treating retrolental fibroplasia, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist to the eye, such that the formation of blood vessels is inhibited. The compound may be administered topically, via intravitreal injection and/or via intraocular implants.

Additionally, disorders which can be treated with the polynucleotides, polypeptides, agonists and/or antagonists include, but are not limited to, hemangioma, arthritis, psoriasis, angiofibroma, atherosclerotic plaques, delayed wound healing, granulations, hemophilic joints, hypertrophic scars, nonunion fractures, Osler-Weber syndrome, pyogenic granuloma, scleroderma, trachoma, and vascular adhesions.

Moreover, disorders and/or states, which can be treated, prevented, diagnosed, and/or prognosed with the polynucleotides, polypeptides, agonists and/or antagonists of the invention include, but are not limited to, solid tumors, blood born tumors such as leukemias, tumor metastasis, Kaposi's sarcoma, benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas, rheumatoid arthritis, psoriasis, ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, and uveitis, delayed wound healing, endometriosis, vasculogenesis, granulations, hypertrophic scars (keloids), nonunion fractures, scleroderma, trachoma, vascular adhesions, myocardial angiogenesis, coronary collaterals, cerebral collaterals,

arteriovenous malformations, ischemic limb angiogenesis, Osler-Webber Syndrome, plaque neovascularization, telangiectasia, hemophiliac joints, angiofibroma fibromuscular dysplasia, wound granulation, Crohn's disease, atherosclerosis, birth control agent by preventing vascularization required for embryo implantation

- 5 controlling menstruation, diseases that have angiogenesis as a pathologic consequence such as cat scratch disease (*Rochela minalia quintosa*), ulcers (*Helicobacter pylori*), Bartonellosis and bacillary angiomatosis.

In one aspect of the birth control method, an amount of the compound sufficient to block embryo implantation is administered before or after intercourse and
10 fertilization have occurred, thus providing an effective method of birth control, possibly a "morning after" method. Polynucleotides, polypeptides, agonists and/or agonists may also be used in controlling menstruation or administered as either a peritoneal lavage fluid or for peritoneal implantation in the treatment of endometriosis.

- 15 Polynucleotides, polypeptides, agonists and/or agonists of the present invention may be incorporated into surgical sutures in order to prevent stitch granulomas.

Polynucleotides, polypeptides, agonists and/or agonists may be utilized in a wide variety of surgical procedures. For example, within one aspect of the present
20 invention a compositions (in the form of, for example, a spray or film) may be utilized to coat or spray an area prior to removal of a tumor, in order to isolate normal surrounding tissues from malignant tissue, and/or to prevent the spread of disease to surrounding tissues. Within other aspects of the present invention, compositions (e.g., in the form of a spray) may be delivered via endoscopic procedures in order to coat
25 tumors, or inhibit angiogenesis in a desired locale. Within yet other aspects of the present invention, surgical meshes which have been coated with anti- angiogenic compositions of the present invention may be utilized in any procedure wherein a surgical mesh might be utilized. For example, within one embodiment of the invention a surgical mesh laden with an anti-angiogenic composition may be utilized
30 during abdominal cancer resection surgery (e.g., subsequent to colon resection) in order to provide support to the structure, and to release an amount of the anti-angiogenic factor.

Within further aspects of the present invention, methods are provided for treating tumor excision sites, comprising administering a polynucleotide, polypeptide, agonist and/or antagonist to the resection margins of a tumor subsequent to excision, such that the local recurrence of cancer and the formation of new blood vessels at the site is inhibited. Within one embodiment of the invention, the anti-angiogenic compound is administered directly to the tumor excision site (e.g., applied by swabbing, brushing or otherwise coating the resection margins of the tumor with the anti-angiogenic compound). Alternatively, the anti-angiogenic compounds may be incorporated into known surgical pastes prior to administration. Within particularly preferred embodiments of the invention, the anti-angiogenic compounds are applied after hepatic resections for malignancy, and after neurosurgical operations.

Within one aspect of the present invention, polynucleotides, polypeptides, agonists and/or antagonists may be administered to the resection margin of a wide variety of tumors, including for example, breast, colon, brain and hepatic tumors. For example, within one embodiment of the invention, anti-angiogenic compounds may be administered to the site of a neurological tumor subsequent to excision, such that the formation of new blood vessels at the site are inhibited.

The polynucleotides, polypeptides, agonists and/or antagonists of the present invention may also be administered along with other anti-angiogenic factors.

Representative examples of other anti-angiogenic factors include: Anti-Invasive Factor, retinoic acid and derivatives thereof, paclitaxel, Suramin, Tissue Inhibitor of Metalloproteinase-1, Tissue Inhibitor of Metalloproteinase-2, Plasminogen Activator Inhibitor-1, Plasminogen Activator Inhibitor-2, and various forms of the lighter "d group" transition metals.

Lighter "d group" transition metals include, for example, vanadium, molybdenum, tungsten, titanium, niobium, and tantalum species. Such transition metal species may form transition metal complexes. Suitable complexes of the above-mentioned transition metal species include oxo transition metal complexes.

Representative examples of vanadium complexes include oxo vanadium complexes such as vanadate and vanadyl complexes. Suitable vanadate complexes include metavanadate and orthovanadate complexes such as, for example, ammonium metavanadate, sodium metavanadate, and sodium orthovanadate. Suitable vanadyl

complexes include, for example, vanadyl acetylacetonate and vanadyl sulfate including vanadyl sulfate hydrates such as vanadyl sulfate mono- and trihydrates.

Representative examples of tungsten and molybdenum complexes also include oxo complexes. Suitable oxo tungsten complexes include tungstate and tungsten
 5 oxide complexes. Suitable tungstate complexes include ammonium tungstate, calcium tungstate, sodium tungstate dihydrate, and tungstic acid. Suitable tungsten oxides include tungsten (IV) oxide and tungsten (VI) oxide. Suitable oxo molybdenum complexes include molybdate, molybdenum oxide, and molybdenyl complexes. Suitable molybdate complexes include ammonium molybdate and its
 10 hydrates, sodium molybdate and its hydrates, and potassium molybdate and its hydrates. Suitable molybdenum oxides include molybdenum (VI) oxide, molybdenum (VI) oxide, and molybdic acid. Suitable molybdenyl complexes include, for example, molybdenyl acetylacetonate. Other suitable tungsten and molybdenum complexes include hydroxo derivatives derived from, for example, glycerol, tartaric acid, and
 15 sugars.

A wide variety of other anti-angiogenic factors may also be utilized within the context of the present invention. Representative examples include platelet factor 4; protamine sulphate; sulphated chitin derivatives (prepared from queen crab shells), (Murata et al., Cancer Res. 51:22-26, 1991); Sulphated Polysaccharide Peptidoglycan
 20 Complex (SP- PG) (the function of this compound may be enhanced by the presence of steroids such as estrogen, and tamoxifen citrate); Staurosporine; modulators of matrix metabolism, including for example, proline analogs, cishydroxyproline, d,L-3,4-dehydroproline, Thiaproline, alpha,alpha-dipyridyl, aminopropionitrile fumarate; 4-propyl-5-(4-pyridinyl)-2(3H)-oxazolone; Methotrexate; Mitoxantrone; Heparin;
 25 Interferons; 2 Macroglobulin-serum; ChIMP-3 (Pavloff et al., J. Bio. Chem. 267:17321-17326, 1992); Chymostatin (Tomkinson et al., Biochem J. 286:475-480, 1992); Cyclodextrin Tetradasulfate; Eponemycin; Camptothecin; Fumagillin (Ingber et al., Nature 348:555-557, 1990); Gold Sodium Thiomalate ("GST"; Matsubara and Ziff, J. Clin. Invest. 79:1440-1446, 1987); anticollagenase-serum;
 30 alpha2-antiplasmin (Holmes et al., J. Biol. Chem. 262(4):1659-1664, 1987); Bisantrene (National Cancer Institute); Lobenzarit disodium (N-(2)-carboxyphenyl-4-chloroanthronilic acid disodium or "CCA"; Takeuchi et al., Agents Actions 36:312-

316, 1992); Thalidomide; Angostatic steroid; AGM-1470; carboxynaminolmidazole; and metalloproteinase inhibitors such as BB94.

Diseases at the Cellular Level

5 Diseases associated with increased cell survival or the inhibition of apoptosis that could be treated, prevented, diagnosed, and/or prognosed using polynucleotides or polypeptides, as well as antagonists or agonists of the present invention, include cancers (such as follicular lymphomas, carcinomas with p53 mutations, and hormone-dependent tumors, including, but not limited to colon cancer, cardiac tumors,
10 pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma, lymphoma, endothelioma, osteoblastoma, osteoclastoma, osteosarcoma, chondrosarcoma, adenoma, breast cancer, prostate cancer, Kaposi's sarcoma and ovarian cancer); autoimmune disorders (such as, multiple sclerosis, Sjogren's
15 syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) and viral infections (such as herpes viruses, pox viruses and adenoviruses), inflammation, graft v. host disease, acute graft rejection, and chronic graft rejection.

20 In preferred embodiments, polynucleotides, polypeptides, and/or antagonists of the invention are used to inhibit growth, progression, and/or metasis of cancers, in particular those listed above.

Additional diseases or conditions associated with increased cell survival that could be treated or detected by polynucleotides or polypeptides, or agonists or
25 antagonists of the present invention include, but are not limited to, progression, and/or metastases of malignancies and related disorders such as leukemia (including acute leukemias (e.g., acute lymphocytic leukemia, acute myelocytic leukemia (including myeloblastic, promyelocytic, myelomonocytic, monocytic, and erythroleukemia)) and chronic leukemias (e.g., chronic myelocytic (granulocytic) leukemia and chronic
30 lymphocytic leukemia)), polycythemia vera, lymphomas (e.g., Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors including, but not limited to, sarcomas and

carcinomas such as fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, menangioma, melanoma, neuroblastoma, and retinoblastoma.

Diseases associated with increased apoptosis that could be treated, prevented, diagnosed, and/or prognosed using polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, include, but are not limited to, AIDS; neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, Retinitis pigmentosa, Cerebellar degeneration and brain tumor or prior associated disease); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) myelodysplastic syndromes (such as aplastic anemia), graft v. host disease, ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), liver injury (e.g., hepatitis related liver injury, ischemia/reperfusion injury, cholestasis (bile duct injury) and liver cancer); toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia.

Wound Healing and Epithelial Cell Proliferation

In accordance with yet a further aspect of the present invention, there is provided a process for utilizing polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, for therapeutic purposes, for example, to

stimulate epithelial cell proliferation and basal keratinocytes for the purpose of wound healing, and to stimulate hair follicle production and healing of dermal wounds.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may be clinically useful in stimulating wound healing including surgical
5 wounds, excisional wounds, deep wounds involving damage of the dermis and epidermis, eye tissue wounds, dental tissue wounds, oral cavity wounds, diabetic ulcers, dermal ulcers, cubitus ulcers, arterial ulcers, venous stasis ulcers, burns resulting from heat exposure or chemicals, and other abnormal wound healing conditions such as uremia, malnutrition, vitamin deficiencies and complications
10 associated with systemic treatment with steroids, radiation therapy and antineoplastic drugs and antimetabolites. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to promote dermal reestablishment subsequent to dermal loss

Polynucleotides or polypeptides, as well as agonists or antagonists of the
15 present invention, could be used to increase the adherence of skin grafts to a wound bed and to stimulate re-epithelialization from the wound bed. The following are types of grafts that polynucleotides or polypeptides, agonists or antagonists of the present invention, could be used to increase adherence to a wound bed: autografts, artificial skin, allografts, autodermic graft, autoepdermic grafts, avacular grafts, Blair-Brown
20 grafts, bone graft, brephoplastic grafts, cutis graft, delayed graft, dermic graft, epidermic graft, fascia graft, full thickness graft, heterologous graft, xenograft, homologous graft, hyperplastic graft, lamellar graft, mesh graft, mucosal graft, Ollier-Thiersch graft, omenpal graft, patch graft, pedicle graft, penetrating graft, split skin graft, thick split graft. Polynucleotides or polypeptides, as well as agonists or
25 antagonists of the present invention, can be used to promote skin strength and to improve the appearance of aged skin.

It is believed that polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, will also produce changes in hepatocyte proliferation, and epithelial cell proliferation in the lung, breast, pancreas, stomach,
30 small intestine, and large intestine. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could promote proliferation of epithelial cells such as sebocytes, hair follicles, hepatocytes, type II pneumocytes,

mucin-producing goblet cells, and other epithelial cells and their progenitors contained within the skin, lung, liver, and gastrointestinal tract. Polynucleotides or polypeptides, agonists or antagonists of the present invention, may promote proliferation of endothelial cells, keratinocytes, and basal keratinocytes.

5 Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could also be used to reduce the side effects of gut toxicity that result from radiation, chemotherapy treatments or viral infections. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may have a cytoprotective effect on the small intestine mucosa. Polynucleotides or polypeptides,
10 as well as agonists or antagonists of the present invention, may also stimulate healing of mucositis (mouth ulcers) that result from chemotherapy and viral infections.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could further be used in full regeneration of skin in full and partial thickness skin defects, including burns, (i.e., repopulation of hair follicles, sweat
15 glands, and sebaceous glands), treatment of other skin defects such as psoriasis. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to treat epidermolysis bullosa, a defect in adherence of the epidermis to the underlying dermis which results in frequent, open and painful blisters by accelerating reepithelialization of these lesions. Polynucleotides or polypeptides,
20 as well as agonists or antagonists of the present invention, could also be used to treat gastric and duodenal ulcers and help heal by scar formation of the mucosal lining and regeneration of glandular mucosa and duodenal mucosal lining more rapidly. Inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis, are diseases which result in destruction of the mucosal surface of the small or large
25 intestine, respectively. Thus, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to promote the resurfacing of the mucosal surface to aid more rapid healing and to prevent progression of inflammatory bowel disease. Treatment with polynucleotides or polypeptides, agonists or antagonists of the present invention, is expected to have a significant effect on the
30 production of mucus throughout the gastrointestinal tract and could be used to protect the intestinal mucosa from injurious substances that are ingested or following surgery.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to treat diseases associate with the under expression.

Moreover, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to prevent and heal damage to the lungs due to various pathological states. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, which could stimulate proliferation and differentiation and promote the repair of alveoli and bronchiolar epithelium to prevent or treat acute or chronic lung damage. For example, emphysema, which results in the progressive loss of aveoli, and inhalation injuries, i.e., resulting from smoke inhalation and burns, that cause necrosis of the bronchiolar epithelium and alveoli could be effectively treated using polynucleotides or polypeptides, agonists or antagonists of the present invention. Also, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to stimulate the proliferation of and differentiation of type II pneumocytes, which may help treat or prevent disease such as hyaline membrane diseases, such as infant respiratory distress syndrome and bronchopulmonary displasia, in premature infants.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could stimulate the proliferation and differentiation of hepatocytes and, thus, could be used to alleviate or treat liver diseases and pathologies such as fulminant liver failure caused by cirrhosis, liver damage caused by viral hepatitis and toxic substances (i.e., acetaminophen, carbon tetraholoride and other hepatotoxins known in the art).

In addition, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used treat or prevent the onset of diabetes mellitus. In patients with newly diagnosed Types I and II diabetes, where some islet cell function remains, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to maintain the islet function so as to alleviate, delay or prevent permanent manifestation of the disease. Also, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used as an auxiliary in islet cell transplantation to improve or promote islet cell function.

Neural Activity and Neurological Diseases

The polynucleotides, polypeptides and agonists or antagonists of the invention may be used for the diagnosis and/or treatment of diseases, disorders, damage or injury of the brain and/or nervous system. Nervous system disorders that can be

5 treated with the compositions of the invention (e.g., polypeptides, polynucleotides, and/or agonists or antagonists), include, but are not limited to, nervous system injuries, and diseases or disorders which result in either a disconnection of axons, a diminution or degeneration of neurons, or demyelination. Nervous system lesions which may be treated in a patient (including human and non-human mammalian

10 patients) according to the methods of the invention, include but are not limited to, the following lesions of either the central (including spinal cord, brain) or peripheral nervous systems: (1) ischemic lesions, in which a lack of oxygen in a portion of the nervous system results in neuronal injury or death, including cerebral infarction or ischemia, or spinal cord infarction or ischemia; (2) traumatic lesions, including

15 lesions caused by physical injury or associated with surgery, for example, lesions which sever a portion of the nervous system, or compression injuries; (3) malignant lesions, in which a portion of the nervous system is destroyed or injured by malignant tissue which is either a nervous system associated malignancy or a malignancy derived from non-nervous system tissue; (4) infectious lesions, in which a portion of

20 the nervous system is destroyed or injured as a result of infection, for example, by an abscess or associated with infection by human immunodeficiency virus, herpes zoster, or herpes simplex virus or with Lyme disease, tuberculosis, or syphilis; (5) degenerative lesions, in which a portion of the nervous system is destroyed or injured as a result of a degenerative process including but not limited to, degeneration

25 associated with Parkinson's disease, Alzheimer's disease, Huntington's chorea, or amyotrophic lateral sclerosis (ALS); (6) lesions associated with nutritional diseases or disorders, in which a portion of the nervous system is destroyed or injured by a nutritional disorder or disorder of metabolism including, but not limited to, vitamin B12 deficiency, folic acid deficiency, Wernicke disease, tobacco-alcohol amblyopia,

30 Marchiafava-Bignami disease (primary degeneration of the corpus callosum), and alcoholic cerebellar degeneration; (7) neurological lesions associated with systemic diseases including, but not limited to, diabetes (diabetic neuropathy, Bell's palsy),

systemic lupus erythematosus, carcinoma, or sarcoidosis; (8) lesions caused by toxic substances including alcohol, lead, or particular neurotoxins; and (9) demyelinated lesions in which a portion of the nervous system is destroyed or injured by a demyelinating disease including, but not limited to, multiple sclerosis, human
5 immunodeficiency virus-associated myelopathy, transverse myelopathy or various etiologies, progressive multifocal leukoencephalopathy, and central pontine myelinolysis.

In one embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to protect neural cells from the damaging effects
10 of hypoxia. In a further preferred embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to protect neural cells from the damaging effects of cerebral hypoxia. According to this embodiment, the compositions of the invention are used to treat or prevent neural cell injury associated with cerebral hypoxia. In one non-exclusive aspect of this embodiment, the
15 polypeptides, polynucleotides, or agonists or antagonists of the invention, are used to treat or prevent neural cell injury associated with cerebral ischemia. In another non-exclusive aspect of this embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent neural cell injury associated with cerebral infarction.

20 In another preferred embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent neural cell injury associated with a stroke. In a specific embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent cerebral neural cell injury associated with a stroke.

25 In another preferred embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent neural cell injury associated with a heart attack. In a specific embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent cerebral neural cell injury associated with a heart attack.

30 The compositions of the invention which are useful for treating or preventing a nervous system disorder may be selected by testing for biological activity in promoting the survival or differentiation of neurons. For example, and not by way of

limitation, compositions of the invention which elicit any of the following effects may be useful according to the invention: (1) increased survival time of neurons in culture either in the presence or absence of hypoxia or hypoxic conditions; (2) increased sprouting of neurons in culture or *in vivo*; (3) increased production of a neuron-associated molecule in culture or *in vivo*, e.g., choline acetyltransferase or acetylcholinesterase with respect to motor neurons; or (4) decreased symptoms of neuron dysfunction *in vivo*. Such effects may be measured by any method known in the art. In preferred, non-limiting embodiments, increased survival of neurons may routinely be measured using a method set forth herein or otherwise known in the art, such as, for example, in Zhang *et al.*, *Proc Natl Acad Sci USA* 97:3637-42 (2000) or in Arakawa *et al.*, *J. Neurosci.*, 10:3507-15 (1990); increased sprouting of neurons may be detected by methods known in the art, such as, for example, the methods set forth in Pestronk *et al.*, *Exp. Neurol.*, 70:65-82 (1980), or Brown *et al.*, *Ann. Rev. Neurosci.*, 4:17-42 (1981); increased production of neuron-associated molecules may be measured by bioassay, enzymatic assay, antibody binding, Northern blot assay, etc., using techniques known in the art and depending on the molecule to be measured; and motor neuron dysfunction may be measured by assessing the physical manifestation of motor neuron disorder, e.g., weakness, motor neuron conduction velocity, or functional disability.

In specific embodiments, motor neuron disorders that may be treated according to the invention include, but are not limited to, disorders such as infarction, infection, exposure to toxin, trauma, surgical damage, degenerative disease or malignancy that may affect motor neurons as well as other components of the nervous system, as well as disorders that selectively affect neurons such as amyotrophic lateral sclerosis, and including, but not limited to, progressive spinal muscular atrophy, progressive bulbar palsy, primary lateral sclerosis, infantile and juvenile muscular atrophy, progressive bulbar paralysis of childhood (Fazio-Londe syndrome), poliomyelitis and the post polio syndrome, and Hereditary Motorsensory Neuropathy (Charcot-Marie-Tooth Disease).

Further, polypeptides or polynucleotides of the invention may play a role in neuronal survival; synapse formation; conductance; neural differentiation, etc. Thus, compositions of the invention (including polynucleotides, polypeptides, and agonists

or antagonists) may be used to diagnose and/or treat or prevent diseases or disorders associated with these roles, including, but not limited to, learning and/or cognition disorders. The compositions of the invention may also be useful in the treatment or prevention of neurodegenerative disease states and/or behavioural disorders. Such neurodegenerative disease states and/or behavioral disorders include, but are not limited to, Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, compositions of the invention may also play a role in the treatment, prevention and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders.

Additionally, polypeptides, polynucleotides and/or agonists or antagonists of the invention, may be useful in protecting neural cells from diseases, damage, disorders, or injury, associated with cerebrovascular disorders including, but not limited to, carotid artery diseases (e.g., carotid artery thrombosis, carotid stenosis, or Moyamoya Disease), cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformations, cerebral artery diseases, cerebral embolism and thrombosis (e.g., carotid artery thrombosis, sinus thrombosis, or Wallenberg's Syndrome), cerebral hemorrhage (e.g., epidural or subdural hematoma, or subarachnoid hemorrhage), cerebral infarction, cerebral ischemia (e.g., transient cerebral ischemia, Subclavian Steal Syndrome, or vertebrobasilar insufficiency), vascular dementia (e.g., multi-infarct), leukomalacia, periventricular, and vascular headache (e.g., cluster headache or migraines).

In accordance with yet a further aspect of the present invention, there is provided a process for utilizing polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, for therapeutic purposes, for example, to stimulate neurological cell proliferation and/or differentiation. Therefore, polynucleotides, polypeptides, agonists and/or antagonists of the invention may be used to treat and/or detect neurologic diseases. Moreover, polynucleotides or polypeptides, or agonists or antagonists of the invention, can be used as a marker or detector of a particular nervous system disease or disorder.

Examples of neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include brain diseases, such as metabolic brain diseases which includes phenylketonuria such as maternal phenylketonuria, pyruvate carboxylase deficiency, pyruvate dehydrogenase complex deficiency, Wernicke's Encephalopathy, brain edema, brain neoplasms such as cerebellar neoplasms which include infratentorial neoplasms, cerebral ventricle neoplasms such as choroid plexus neoplasms, hypothalamic neoplasms, supratentorial neoplasms, canavan disease, cerebellar diseases such as cerebellar ataxia which include spinocerebellar degeneration such as ataxia telangiectasia, cerebellar dyssynergia, Friederich's Ataxia, Machado-Joseph Disease, olivopontocerebellar atrophy, cerebellar neoplasms such as infratentorial neoplasms, diffuse cerebral sclerosis such as encephalitis periaxialis, globoid cell leukodystrophy, metachromatic leukodystrophy and subacute sclerosing panencephalitis.

Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include cerebrovascular disorders (such as carotid artery diseases which include carotid artery thrombosis, carotid stenosis and Moyamoya Disease), cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformations, cerebral artery diseases, cerebral embolism and thrombosis such as carotid artery thrombosis, sinus thrombosis and Wallenberg's Syndrome, cerebral hemorrhage such as epidural hematoma, subdural hematoma and subarachnoid hemorrhage, cerebral infarction, cerebral ischemia such as transient cerebral ischemia, Subclavian Steal Syndrome and vertebrobasilar insufficiency, vascular dementia such as multi-infarct dementia, periventricular leukomalacia, vascular headache such as cluster headache and migraine.

Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include dementia such as AIDS Dementia Complex, presenile dementia such as Alzheimer's Disease and Creutzfeldt-Jakob Syndrome, senile dementia such as Alzheimer's Disease and progressive supranuclear palsy, vascular dementia such as multi-infarct dementia, encephalitis which include encephalitis periaxialis, viral

encephalitis such as epidemic encephalitis, Japanese Encephalitis, St. Louis Encephalitis, tick-borne encephalitis and West Nile Fever, acute disseminated encephalomyelitis, meningoencephalitis such as uveomeningoencephalitic syndrome, Postencephalitic Parkinson Disease and subacute sclerosing panencephalitis, 5 encephalomalacia such as periventricular leukomalacia, epilepsy such as generalized epilepsy which includes infantile spasms, absence epilepsy, myoclonic epilepsy which includes MERRF Syndrome, tonic-clonic epilepsy, partial epilepsy such as complex partial epilepsy, frontal lobe epilepsy and temporal lobe epilepsy, post-traumatic epilepsy, status epilepticus such as Epilepsia Partialis Continua, and Hallervorden- 10 Spatz Syndrome.

Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include hydrocephalus such as Dandy-Walker Syndrome and normal pressure hydrocephalus, hypothalamic diseases such as hypothalamic neoplasms, cerebral 15 malaria, narcolepsy which includes cataplexy, bulbar poliomyelitis, cerebri pseudotumor, Rett Syndrome, Reye's Syndrome, thalamic diseases, cerebral toxoplasmosis, intracranial tuberculoma and Zellweger Syndrome, central nervous system infections such as AIDS Dementia Complex, Brain Abscess, subdural empyema, encephalomyelitis such as Equine Encephalomyelitis, Venezuelan Equine 20 Encephalomyelitis, Necrotizing Hemorrhagic Encephalomyelitis, Visna, and cerebral malaria.

Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include meningitis such as arachnoiditis, aseptic meningitis such as viral meningitis 25 which includes lymphocytic choriomeningitis, Bacterial meningitis which includes Haemophilus Meningitis, Listeria Meningitis, Meningococcal Meningitis such as Waterhouse-Friderichsen Syndrome, Pneumococcal Meningitis and meningeal tuberculosis, fungal meningitis such as Cryptococcal Meningitis, subdural effusion, meningoencephalitis such as uveomeningoencephalitic syndrome, myelitis such as 30 transverse myelitis, neurosyphilis such as tabes dorsalis, poliomyelitis which includes bulbar poliomyelitis and postpoliomyelitis syndrome, prion diseases (such as

Creutzfeldt-Jakob Syndrome, Bovine Spongiform Encephalopathy, Gerstmann-Straussler Syndrome, Kuru, Scrapie), and cerebral toxoplasmosis.

Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention

5 include central nervous system neoplasms such as brain neoplasms that include cerebellar neoplasms such as infratentorial neoplasms, cerebral ventricle neoplasms such as choroid plexus neoplasms, hypothalamic neoplasms and supratentorial neoplasms, meningeal neoplasms, spinal cord neoplasms which include epidural neoplasms, demyelinating diseases such as Canavan Diseases, diffuse cerebral
10 scleritis which includes adrenoleukodystrophy, encephalitis periaxialis, globoid cell leukodystrophy, diffuse cerebral sclerosis such as metachromatic leukodystrophy, allergic encephalomyelitis, necrotizing hemorrhagic encephalomyelitis, progressive multifocal leukoencephalopathy, multiple sclerosis, central pontine myelinolysis, transverse myelitis, neuromyelitis optica, Scrapie, Swayback, Chronic Fatigue
15 Syndrome, Visna, High Pressure Nervous Syndrome, Meningism, spinal cord diseases such as amyotonia congenita, amyotrophic lateral sclerosis, spinal muscular atrophy such as Werdnig-Hoffmann Disease, spinal cord compression, spinal cord neoplasms such as epidural neoplasms, syringomyelia, Tabes Dorsalis, Stiff-Man Syndrome, mental retardation such as Angelman Syndrome, Cri-du-Chat Syndrome, De Lange's
20 Syndrome, Down Syndrome, Gangliosidoses such as gangliosidoses G(M1), Sandhoff Disease, Tay-Sachs Disease, Hartnup Disease, homocystinuria, Laurence-Moon-Biedl Syndrome, Lesch-Nyhan Syndrome, Maple Syrup Urine Disease, mucopolipidosis such as fucosidosis, neuronal ceroid-lipofuscinosis, oculocerebrorenal syndrome, phenylketonuria such as maternal phenylketonuria, Prader-Willi Syndrome, Rett
25 Syndrome, Rubinstein-Taybi Syndrome, Tuberous Sclerosis, WAGR Syndrome, nervous system abnormalities such as holoprosencephaly, neural tube defects such as anencephaly which includes hydrangencephaly, Arnold-Chairi Deformity, encephalocele, meningocele, meningomyelocele, spinal dysraphism such as spina bifida cystica and spina bifida occulta.

30 Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include hereditary motor and sensory neuropathies which include Charcot-Marie

Disease, Hereditary optic atrophy, Refsum's Disease, hereditary spastic paraplegia, Werdnig-Hoffmann Disease, Hereditary Sensory and Autonomic Neuropathies such as Congenital Analgesia and Familial Dysautonomia, Neurologic manifestations (such as agnosia that include Gerstmann's Syndrome, Amnesia such as retrograde amnesia, apraxia, neurogenic bladder, cataplexy, communicative disorders such as hearing disorders that includes deafness, partial hearing loss, loudness recruitment and tinnitus, language disorders such as aphasia which include agraphia, anomia, broca aphasia, and Wernicke Aphasia, Dyslexia such as Acquired Dyslexia, language development disorders, speech disorders such as aphasia which includes anomia, broca aphasia and Wernicke Aphasia, articulation disorders, communicative disorders such as speech disorders which include dysarthria, echolalia, mutism and stuttering, voice disorders such as aphonia and hoarseness, decerebrate state, delirium, fasciculation, hallucinations, meningism, movement disorders such as angelman syndrome, ataxia, athetosis, chorea, dystonia, hypokinesia, muscle hypotonia, myoclonus, tic, torticollis and tremor, muscle hypertonia such as muscle rigidity such as stiff-man syndrome, muscle spasticity, paralysis such as facial paralysis which includes Herpes Zoster Oticus, Gastroparesis, Hemiplegia, ophthalmoplegia such as diplopia, Duane's Syndrome, Horner's Syndrome, Chronic progressive external ophthalmoplegia such as Kearns Syndrome, Bulbar Paralysis, Tropical Spastic Paraparesis, Paraplegia such as Brown-Sequard Syndrome, quadriplegia, respiratory paralysis and vocal cord paralysis, paresis, phantom limb, taste disorders such as ageusia and dysgeusia, vision disorders such as amblyopia, blindness, color vision defects, diplopia, hemianopsia, scotoma and subnormal vision, sleep disorders such as hypersomnia which includes Kleine-Levin Syndrome, insomnia, and somnambulism, spasm such as trismus, unconsciousness such as coma, persistent vegetative state and syncope and vertigo, neuromuscular diseases such as amyotonia congenita, amyotrophic lateral sclerosis, Lambert-Eaton Myasthenic Syndrome, motor neuron disease, muscular atrophy such as spinal muscular atrophy, Charcot-Marie Disease and Werdnig-Hoffmann Disease, Postpoliomyelitis Syndrome, Muscular Dystrophy, Myasthenia Gravis, Myotonia Atrophica, Myotonia Confenita, Nemaline Myopathy, Familial Periodic Paralysis, Multiplex Paramyoclonus, Tropical Spastic Paraparesis and Stiff-Man Syndrome, peripheral nervous system diseases such as acrodynia,

- amyloid neuropathies, autonomic nervous system diseases such as Adie's Syndrome, Barre-Lieou Syndrome, Familial Dysautonomia, Horner's Syndrome, Reflex Sympathetic Dystrophy and Shy-Drager Syndrome, Cranial Nerve Diseases such as Acoustic Nerve Diseases such as Acoustic Neuroma which includes
- 5 Neurofibromatosis 2, Facial Nerve Diseases such as Facial Neuralgia, Melkersson-Rosenthal Syndrome, ocular motility disorders which includes amblyopia, nystagmus, oculomotor nerve paralysis, ophthalmoplegia such as Duane's Syndrome, Horner's Syndrome, Chronic Progressive External Ophthalmoplegia which includes Kearns Syndrome, Strabismus such as Esotropia and Exotropia, Oculomotor Nerve Paralysis,
- 10 Optic Nerve Diseases such as Optic Atrophy which includes Hereditary Optic Atrophy, Optic Disk Drusen, Optic Neuritis such as Neuromyelitis Optica, Papilledema, Trigeminal Neuralgia, Vocal Cord Paralysis, Demyelinating Diseases such as Neuromyelitis Optica and Swayback, and Diabetic neuropathies such as diabetic foot.
- 15 Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include nerve compression syndromes such as carpal tunnel syndrome, tarsal tunnel syndrome, thoracic outlet syndrome such as cervical rib syndrome, ulnar nerve compression syndrome, neuralgia such as causalgia, cervico-brachial neuralgia, facial
- 20 neuralgia and trigeminal neuralgia, neuritis such as experimental allergic neuritis, optic neuritis, polyneuritis, polyradiculoneuritis and radiculities such as polyradiculitis, hereditary motor and sensory neuropathies such as Charcot-Marie Disease, Hereditary Optic Atrophy, Refsum's Disease, Hereditary Spastic Paraplegia and Werdnig-Hoffmann Disease, Hereditary Sensory and Autonomic Neuropathies
- 25 which include Congenital Analgesia and Familial Dysautonomia, POEMS Syndrome, Sciatica, Gustatory Sweating and Tetany).

Endocrine Disorders

- Polynucleotides or polypeptides, or agonists or antagonists of the present
- 30 invention, may be used to treat, prevent, diagnose, and/or prognose disorders and/or diseases related to hormone imbalance, and/or disorders or diseases of the endocrine

system.

Hormones secreted by the glands of the endocrine system control physical growth, sexual function, metabolism, and other functions. Disorders may be classified in two ways: disturbances in the production of hormones, and the inability of tissues to respond to hormones. The etiology of these hormone imbalance or endocrine system diseases, disorders or conditions may be genetic, somatic, such as cancer and some autoimmune diseases, acquired (e.g., by chemotherapy, injury or toxins), or infectious. Moreover, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention can be used as a marker or detector of a particular disease or disorder related to the endocrine system and/or hormone imbalance.

Endocrine system and/or hormone imbalance and/or diseases encompass disorders of uterine motility including, but not limited to: complications with pregnancy and labor (e.g., pre-term labor, post-term pregnancy, spontaneous abortion, and slow or stopped labor); and disorders and/or diseases of the menstrual cycle (e.g., dysmenorrhea and endometriosis).

Endocrine system and/or hormone imbalance disorders and/or diseases include disorders and/or diseases of the pancreas, such as, for example, diabetes mellitus, diabetes insipidus, congenital pancreatic agenesis, pheochromocytoma--islet cell tumor syndrome; disorders and/or diseases of the adrenal glands such as, for example, Addison's Disease, corticosteroid deficiency, virilizing disease, hirsutism, Cushing's Syndrome, hyperaldosteronism, pheochromocytoma; disorders and/or diseases of the pituitary gland, such as, for example, hyperpituitarism, hypopituitarism, pituitary dwarfism, pituitary adenoma, panhypopituitarism, acromegaly, gigantism; disorders and/or diseases of the thyroid, including but not limited to, hyperthyroidism, hypothyroidism, Plummer's disease, Graves' disease (toxic diffuse goiter), toxic nodular goiter, thyroiditis (Hashimoto's thyroiditis, subacute granulomatous thyroiditis, and silent lymphocytic thyroiditis), Pendred's syndrome, myxedema, cretinism, thyrotoxicosis, thyroid hormone coupling defect, thymic aplasia, Hurthle cell tumours of the thyroid, thyroid cancer, thyroid carcinoma, Medullary thyroid carcinoma; disorders and/or diseases of the parathyroid, such as, for example, hyperparathyroidism, hypoparathyroidism; disorders and/or diseases of the hypothalamus.

In specific embodiments, the polynucleotides and/or polypeptides corresponding to this gene and/or agonists or antagonists of those polypeptides (including antibodies) as well as fragments and variants of those polynucleotides, polypeptides, agonists and antagonists, may be used to diagnose, prognose, treat, prevent, or ameliorate diseases and disorders associated with aberrant glucose metabolism or glucose uptake into cells.

In a specific embodiment, the polynucleotides and/or polypeptides corresponding to this gene and/or agonists and/or antagonists thereof may be used to diagnose, prognose, treat, prevent, and/or ameliorate type I diabetes mellitus (insulin dependent diabetes mellitus, IDDM).

In another embodiment, the polynucleotides and/or polypeptides corresponding to this gene and/or agonists and/or antagonists thereof may be used to diagnose, prognose, treat, prevent, and/or ameliorate type II diabetes mellitus (insulin resistant diabetes mellitus).

Additionally, in other embodiments, the polynucleotides and/or polypeptides corresponding to this gene and/or antagonists thereof (especially neutralizing or antagonistic antibodies) may be used to diagnose, prognose, treat, prevent, and/or ameliorate conditions associated with (type I or type II) diabetes mellitus, including, but not limited to, diabetic ketoacidosis, diabetic coma, nonketotic hyperglycemic-hyperosmolar coma, seizures, mental confusion, drowsiness, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section), dyslipidemia, kidney disease (e.g., renal failure, nephropathy other diseases and disorders as described in the "Renal Disorders" section), nerve damage, neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infections (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture.

In other embodiments, the polynucleotides and/or polypeptides corresponding to this gene and/or agonists or antagonists thereof are administered to an animal, preferably a mammal, and most preferably a human, in order to regulate the animal's weight. In specific embodiments the polynucleotides and/or polypeptides

corresponding to this gene and/or agonists or antagonists thereof are administered to an animal, preferably a mammal, and most preferably a human, in order to control the animal's weight by modulating a biochemical pathway involving insulin. In still other embodiments the polynucleotides and/or polypeptides corresponding to this gene
5 and/or agonists or antagonists thereof are administered to an animal, preferably a mammal, and most preferably a human, in order to control the animal's weight by modulating a biochemical pathway involving insulin-like growth factor.

In addition, endocrine system and/or hormone imbalance disorders and/or diseases may also include disorders and/or diseases of the testes or ovaries, including
10 cancer. Other disorders and/or diseases of the testes or ovaries further include, for example, ovarian cancer, polycystic ovary syndrome, Klinefelter's syndrome, vanishing testes syndrome (bilateral anorchia), congenital absence of Leydig's cells, cryptorchidism, Noonan's syndrome, myotonic dystrophy, capillary haemangioma of the testis (benign), neoplasias of the testis and neo-testis.

Moreover, endocrine system and/or hormone imbalance disorders and/or
15 diseases may also include disorders and/or diseases such as, for example, polyglandular deficiency syndromes, pheochromocytoma, neuroblastoma, multiple Endocrine neoplasia, and disorders and/or cancers of endocrine tissues.

In another embodiment, a polypeptide of the invention, or polynucleotides,
20 antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to diagnose, prognose, prevent, and/or treat endocrine diseases and/or disorders associated with the tissue(s) in which the polypeptide of the invention is expressed, including one, two, three, four, five, or more tissues disclosed in Table 1B, column 8 (Tissue Distribution Library Code).

25

Reproductive System Disorders

The polynucleotides or polypeptides, or agonists or antagonists of the invention may be used for the diagnosis, treatment, or prevention of diseases and/or disorders of the reproductive system. Reproductive system disorders that can be
30 treated by the compositions of the invention, include, but are not limited to, reproductive system injuries, infections, neoplastic disorders, congenital defects, and

diseases or disorders which result in infertility, complications with pregnancy, labor, or parturition, and postpartum difficulties.

Reproductive system disorders and/or diseases include diseases and/or disorders of the testes, including testicular atrophy, testicular feminization, cryptorchism (unilateral and bilateral), anorchia, ectopic testis, epididymitis and orchitis (typically resulting from infections such as, for example, gonorrhea, mumps, tuberculosis, and syphilis), testicular torsion, vasitis nodosa, germ cell tumors (e.g., seminomas, embryonal cell carcinomas, teratocarcinomas, choriocarcinomas, yolk sac tumors, and teratomas), stromal tumors (e.g., Leydig cell tumors), hydrocele, hematocele, varicocele, spermatocele, inguinal hernia, and disorders of sperm production (e.g., immotile cilia syndrome, aspermia, asthenozoospermia, azoospermia, oligospermia, and teratozoospermia).

Reproductive system disorders also include disorders of the prostate gland, such as acute non-bacterial prostatitis, chronic non-bacterial prostatitis, acute bacterial prostatitis, chronic bacterial prostatitis, prostatodystonia, prostatosis, granulomatous prostatitis, malacoplakia, benign prostatic hypertrophy or hyperplasia, and prostate neoplastic disorders, including adenocarcinomas, transitional cell carcinomas, ductal carcinomas, and squamous cell carcinomas.

Additionally, the compositions of the invention may be useful in the diagnosis, treatment, and/or prevention of disorders or diseases of the penis and urethra, including inflammatory disorders, such as balanoposthitis, balanitis xerotica obliterans, phimosis, paraphimosis, syphilis, herpes simplex virus, gonorrhea, non-gonococcal urethritis, chlamydia, mycoplasma, trichomonas, HIV, AIDS, Reiter's syndrome, condyloma acuminatum, condyloma latum, and pearly penile papules; urethral abnormalities, such as hypospadias, epispadias, and phimosis; premalignant lesions, including Erythroplasia of Queyrat, Bowen's disease, Bowenoid papulosis, giant condyloma of Buscke-Lowenstein, and verrucous carcinoma; penile cancers, including squamous cell carcinomas, carcinoma in situ, verrucous carcinoma, and disseminated penile carcinoma; urethral neoplastic disorders, including penile urethral carcinoma, bulbomembranous urethral carcinoma, and prostatic urethral carcinoma; and erectile disorders, such as priapism, Peyronie's disease, erectile dysfunction, and impotence.

Moreover, diseases and/or disorders of the vas deferens include vasculitis and CBAVD (congenital bilateral absence of the vas deferens); additionally, the polynucleotides, polypeptides, and agonists or antagonists of the present invention may be used in the diagnosis, treatment, and/or prevention of diseases and/or disorders of the seminal vesicles, including hydatid disease, congenital chloride diarrhea, and polycystic kidney disease.

Other disorders and/or diseases of the male reproductive system include, for example, Klinefelter's syndrome, Young's syndrome, premature ejaculation, diabetes mellitus, cystic fibrosis, Kartagener's syndrome, high fever, multiple sclerosis, and gynecomastia.

Further, the polynucleotides, polypeptides, and agonists or antagonists of the present invention may be used in the diagnosis, treatment, and/or prevention of diseases and/or disorders of the vagina and vulva, including bacterial vaginosis, candida vaginitis, herpes simplex virus, chancroid, granuloma inguinale, lymphogranuloma venereum, scabies, human papillomavirus, vaginal trauma, vulvar trauma, adenosis, chlamydia vaginitis, gonorrhea, trichomonas vaginitis, condyloma acuminatum, syphilis, molluscum contagiosum, atrophic vaginitis, Paget's disease, lichen sclerosus, lichen planus, vulvodynia, toxic shock syndrome, vaginismus, vulvovaginitis, vulvar vestibulitis, and neoplastic disorders, such as squamous cell hyperplasia, clear cell carcinoma, basal cell carcinoma, melanomas, cancer of Bartholin's gland, and vulvar intraepithelial neoplasia.

Disorders and/or diseases of the uterus include dysmenorrhea, retroverted uterus, endometriosis, fibroids, adenomyosis, anovulatory bleeding, amenorrhea, Cushing's syndrome, hydatidiform moles, Asherman's syndrome, premature menopause, precocious puberty, uterine polyps, dysfunctional uterine bleeding (e.g., due to aberrant hormonal signals), and neoplastic disorders, such as adenocarcinomas, leiomyosarcomas, and sarcomas. Additionally, the polypeptides, polynucleotides, or agonists or antagonists of the invention may be useful as a marker or detector of, as well as in the diagnosis, treatment, and/or prevention of congenital uterine abnormalities, such as bicornuate uterus, septate uterus, simple unicornuate uterus, unicornuate uterus with a noncavitary rudimentary horn, unicornuate uterus with a

non-communicating cavitary rudimentary horn, unicornuate uterus with a communicating cavitary horn, arcuate uterus, uterine didelphys, and T-shaped uterus.

Ovarian diseases and/or disorders include anovulation, polycystic ovary syndrome (Stein-Leventhal syndrome), ovarian cysts, ovarian hypofunction, ovarian
5 insensitivity to gonadotropins, ovarian overproduction of androgens, right ovarian vein syndrome, amenorrhea, hirsutism, and ovarian cancer (including, but not limited to, primary and secondary cancerous growth, Sertoli-Leydig tumors, endometriod carcinoma of the ovary, ovarian papillary serous adenocarcinoma, ovarian mucinous adenocarcinoma, and Ovarian Krukenberg tumors).

10 Cervical diseases and/or disorders include cervicitis, chronic cervicitis, mucopurulent cervicitis, cervical dysplasia, cervical polyps, Nabothian cysts, cervical erosion, cervical incompetence, and cervical neoplasms (including, for example, cervical carcinoma, squamous metaplasia, squamous cell carcinoma, adenosquamous cell neoplasia, and columnar cell neoplasia).

15 Additionally, diseases and/or disorders of the reproductive system include disorders and/or diseases of pregnancy, including miscarriage and stillbirth, such as early abortion, late abortion, spontaneous abortion, induced abortion, therapeutic abortion, threatened abortion, missed abortion, incomplete abortion, complete abortion, habitual abortion, missed abortion, and septic abortion; ectopic pregnancy,
20 anemia, Rh incompatibility, vaginal bleeding during pregnancy, gestational diabetes, intrauterine growth retardation, polyhydramnios, HELLP syndrome, abruptio placentae, placenta previa, hyperemesis, preeclampsia, eclampsia, herpes gestationis, and urticaria of pregnancy. Additionally, the polynucleotides, polypeptides, and agonists or antagonists of the present invention may be used in the diagnosis,
25 treatment, and/or prevention of diseases that can complicate pregnancy, including heart disease, heart failure, rheumatic heart disease, congenital heart disease, mitral valve prolapse, high blood pressure, anemia, kidney disease, infectious disease (e.g., rubella, cytomegalovirus, toxoplasmosis, infectious hepatitis, chlamydia, HIV, AIDS, and genital herpes), diabetes mellitus, Graves' disease, thyroiditis, hypothyroidism,
30 Hashimoto's thyroiditis, chronic active hepatitis, cirrhosis of the liver, primary biliary cirrhosis, asthma, systemic lupus erythematosus, rheumatoid arthritis, myasthenia

gravis, idiopathic thrombocytopenic purpura, appendicitis, ovarian cysts, gallbladder disorders, and obstruction of the intestine.

Complications associated with labor and parturition include premature rupture of the membranes, pre-term labor, post-term pregnancy, postmaturity, labor that
5 progresses too slowly, fetal distress (e.g., abnormal heart rate (fetal or maternal), breathing problems, and abnormal fetal position), shoulder dystocia, prolapsed umbilical cord, amniotic fluid embolism, and aberrant uterine bleeding.

Further, diseases and/or disorders of the postdelivery period, including endometritis, myometritis, parametritis, peritonitis, pelvic thrombophlebitis,
10 pulmonary embolism, endotoxemia, pyelonephritis, saphenous thrombophlebitis, mastitis, cystitis, postpartum hemorrhage, and inverted uterus.

Other disorders and/or diseases of the female reproductive system that may be diagnosed, treated, and/or prevented by the polynucleotides, polypeptides, and agonists or antagonists of the present invention include, for example, Turner's
15 syndrome, pseudohermaphroditism, premenstrual syndrome, pelvic inflammatory disease, pelvic congestion (vascular engorgement), frigidity, anorgasmia, dyspareunia, ruptured fallopian tube, and Mittelschmerz.

Infectious Disease

20 Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention can be used to treat or detect infectious agents. For example, by increasing the immune response, particularly increasing the proliferation and differentiation of B and/or T cells, infectious diseases may be treated. The immune response may be increased by either enhancing an existing immune response, or by
25 initiating a new immune response. Alternatively, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may also directly inhibit the infectious agent, without necessarily eliciting an immune response.

Viruses are one example of an infectious agent that can cause disease or symptoms that can be treated or detected by a polynucleotide or polypeptide and/or
30 agonist or antagonist of the present invention. Examples of viruses, include, but are not limited to Examples of viruses, include, but are not limited to the following DNA and RNA viruses and viral families: Arbovirus, Adenoviridae, Arenaviridae,

Arterivirus, Birnaviridae, Bunyaviridae, Caliciviridae, Circoviridae, Coronaviridae, Dengue, EBV, HIV, Flaviviridae, Hepadnaviridae (Hepatitis), Herpesviridae (such as, Cytomegalovirus, Herpes Simplex, Herpes Zoster), Mononegavirus (e.g., Paramyxoviridae, Morbillivirus, Rhabdoviridae), Orthomyxoviridae (e.g., Influenza A, Influenza B, and parainfluenza), Papilloma virus, Papovaviridae, Parvoviridae, Picornaviridae, Poxviridae (such as Smallpox or Vaccinia), Reoviridae (e.g., Rotavirus), Retroviridae (HTLV-I, HTLV-II, Lentivirus), and Togaviridae (e.g., Rubivirus). Viruses falling within these families can cause a variety of diseases or symptoms, including, but not limited to: arthritis, bronchiolitis, respiratory syncytial virus, encephalitis, eye infections (e.g., conjunctivitis, keratitis), chronic fatigue syndrome, hepatitis (A, B, C, E, Chronic Active, Delta), Japanese B encephalitis, Junin, Chikungunya, Rift Valley fever, yellow fever, meningitis, opportunistic infections (e.g., AIDS), pneumonia, Burkitt's Lymphoma, chickenpox, hemorrhagic fever, Measles, Mumps, Parainfluenza, Rabies, the common cold, Polio, leukemia, Rubella, sexually transmitted diseases; skin diseases (e.g., Kaposi's, warts), and viremia. polynucleotides or polypeptides, or agonists or antagonists of the invention; can be used to treat or detect any of these symptoms or diseases. In specific embodiments, polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat: meningitis, Dengue, EBV, and/or hepatitis (e.g., hepatitis B). In an additional specific embodiment polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat patients nonresponsive to one or more other commercially available hepatitis vaccines. In a further specific embodiment polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat AIDS.

Similarly, bacterial and fungal agents that can cause disease or symptoms and that can be treated or detected by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention include, but not limited to, the following Gram-Negative and Gram-positive bacteria, bacterial families, and fungi: Actinomyces (e.g., *Nocardia*), Acinetobacter, *Cryptococcus neoformans*, Aspergillus, Bacillaceae (e.g., *Bacillus anthracis*), Bacteroides (e.g., *Bacteroides fragilis*), Blastomycosis, Bordetella, Borrelia (e.g., *Borrelia burgdorferi*), Brucella, Candida, Campylobacter, Chlamydia, Clostridium (e.g., *Clostridium botulinum*, *Clostridium difficile*,

Clostridium perfringens, *Clostridium tetani*), *Coccidioides*, *Corynebacterium* (e.g., *Corynebacterium diphtheriae*), *Cryptococcus*, *Dermatocycoses*, *E. coli* (e.g., Enterotoxigenic *E. coli* and Enterohemorrhagic *E. coli*), *Enterobacter* (e.g., *Enterobacter aerogenes*), *Enterobacteriaceae* (*Klebsiella*, *Salmonella* (e.g., *Salmonella typhi*, *Salmonella enteritidis*, *Salmonella typhi*), *Serratia*, *Yersinia*, *Shigella*), *Erysipelothrix*, *Haemophilus* (e.g., *Haemophilus influenza* type B), *Helicobacter*, *Legionella* (e.g., *Legionella pneumophila*), *Leptospira*, *Listeria* (e.g., *Listeria monocytogenes*), *Mycoplasma*, *Mycobacterium* (e.g., *Mycobacterium leprae* and *Mycobacterium tuberculosis*), *Vibrio* (e.g., *Vibrio cholerae*), *Neisseriaceae* (e.g., *Neisseria gonorrhea*, *Neisseria meningitidis*), *Pasteurellaceae*, *Proteus*, *Pseudomonas* (e.g., *Pseudomonas aeruginosa*), *Rickettsiaceae*, *Spirochetes* (e.g., *Treponema* spp., *Leptospira* spp., *Borrelia* spp.), *Shigella* spp., *Staphylococcus* (e.g., *Staphylococcus aureus*), *Meningioccoccus*, *Pneumococcus* and *Streptococcus* (e.g., *Streptococcus pneumoniae* and Groups A, B, and C *Streptococci*), and *Ureaplasmas*. These

bacterial, parasitic, and fungal families can cause diseases or symptoms, including, but not limited to: antibiotic-resistant infections, bacteremia, endocarditis, septicemia, eye infections (e.g., conjunctivitis), uveitis, tuberculosis, gingivitis, bacterial diarrhea, opportunistic infections (e.g., AIDS related infections), paronychia, prosthesis-related infections, dental caries, Reiter's Disease, respiratory tract infections, such as

Whooping Cough or Empyema, sepsis, Lyme Disease, Cat-Scratch Disease, dysentery, paratyphoid fever, food poisoning, *Legionella* disease, chronic and acute inflammation, erythema, yeast infections, typhoid, pneumonia, gonorrhea, meningitis (e.g., meningitis types A and B), chlamydia, syphilis, diphtheria, leprosy, brucellosis, peptic ulcers, anthrax, spontaneous abortions, birth defects, pneumonia, lung

infections, ear infections, deafness, blindness, lethargy, malaise, vomiting, chronic diarrhea, Crohn's disease, colitis, vaginosis, sterility, pelvic inflammatory diseases, candidiasis, paratuberculosis, tuberculosis, lupus, botulism, gangrene, tetanus, impetigo, Rheumatic Fever, Scarlet Fever, sexually transmitted diseases, skin diseases (e.g., cellulitis, dermatocycoses), toxemia, urinary tract infections, wound infections, noscomial infections. Polynucleotides or polypeptides, agonists or antagonists of the

invention, can be used to treat or detect any of these symptoms or diseases. In

specific embodiments, polynucleotides, polypeptides, agonists or antagonists of the invention are used to treat: tetanus, diphtheria, botulism, and/or meningitis type B.

Moreover, parasitic agents causing disease or symptoms that can be treated, prevented, and/or diagnosed by a polynucleotide or polypeptide and/or agonist or

5 antagonist of the present invention include, but not limited to, the following families or class: Amebiasis, Babesiosis, Coccidiosis, Cryptosporidiosis, Dientamoebiasis, Dourine, Ectoparasitic, Giardiasis, Helminthiasis, Leishmaniasis, Schistosoma, Theileriasis, Toxoplasmosis, Trypanosomiasis, and Trichomonas and Sporozoans (e.g., *Plasmodium virax*, *Plasmodium falciparum*, *Plasmodium malariae* and
10 *Plasmodium ovale*). These parasites can cause a variety of diseases or symptoms, including, but not limited to: Scabies, Trombiculiasis, eye infections, intestinal disease (e.g., dysentery, giardiasis), liver disease, lung disease, opportunistic infections (e.g., AIDS related), malaria, pregnancy complications, and toxoplasmosis. polynucleotides or polypeptides, or agonists or antagonists of the invention, can be
15 used to treat, prevent, and/or diagnose any of these symptoms or diseases. In specific embodiments, polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat, prevent, and/or diagnose malaria.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention of the present invention could either be by administering an
20 effective amount of a polypeptide to the patient, or by removing cells from the patient, supplying the cells with a polynucleotide of the present invention, and returning the engineered cells to the patient (ex vivo therapy). Moreover, the polypeptide or polynucleotide of the present invention can be used as an antigen in a vaccine to raise an immune response against infectious disease.

Regeneration

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention can be used to differentiate, proliferate, and attract cells, leading to the regeneration of tissues. (See, Science 276:59-87 (1997)). The regeneration of
30 tissues could be used to repair, replace, or protect tissue damaged by congenital defects, trauma (wounds, burns, incisions, or ulcers), age, disease (e.g. osteoporosis,

osteocarthritis, periodontal disease, liver failure), surgery, including cosmetic plastic surgery, fibrosis, reperfusion injury, or systemic cytokine damage.

Tissues that could be regenerated using the present invention include organs (e.g., pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal
5 or cardiac), vasculature (including vascular and lymphatics), nervous, hematopoietic, and skeletal (bone, cartilage, tendon, and ligament) tissue. Preferably, regeneration occurs without or decreased scarring. Regeneration also may include angiogenesis.

Moreover, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may increase regeneration of tissues difficult to heal. For
10 example, increased tendon/ligament regeneration would quicken recovery time after damage. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention could also be used prophylactically in an effort to avoid damage. Specific diseases that could be treated include of tendinitis, carpal tunnel syndrome, and other tendon or ligament defects. A further example of tissue regeneration of
15 non-healing wounds includes pressure ulcers, ulcers associated with vascular insufficiency, surgical, and traumatic wounds.

Similarly, nerve and brain tissue could also be regenerated by using polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, to proliferate and differentiate nerve cells. Diseases that could be treated
20 using this method include central and peripheral nervous system diseases, neuropathies, or mechanical and traumatic disorders (e.g., spinal cord disorders, head trauma, cerebrovascular disease, and stoke). Specifically, diseases associated with peripheral nerve injuries, peripheral neuropathy (e.g., resulting from chemotherapy or other medical therapies), localized neuropathies, and central nervous system diseases
25 (e.g., Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome), could all be treated using the polynucleotides or polypeptides, as well as agonists or antagonists of the present invention.

30 **Gastrointestinal Disorders**

Polynucleotides or polypeptides, or agonists or antagonists of the present invention, may be used to treat, prevent, diagnose, and/or prognose gastrointestinal

disorders, including inflammatory diseases and/or conditions, infections, cancers (e.g., intestinal neoplasms (carcinoid tumor of the small intestine, non-Hodgkin's lymphoma of the small intestine, small bowel lymphoma)), and ulcers, such as peptic ulcers.

5 Gastrointestinal disorders include dysphagia, odynophagia, inflammation of the esophagus, peptic esophagitis, gastric reflux, submucosal fibrosis and stricturing, Mallory-Weiss lesions, leiomyomas, lipomas, epidermal cancers, adeoncarcinomas, gastric retention disorders, gastroenteritis, gastric atrophy, gastric/stomach cancers, polyps of the stomach, autoimmune disorders such as pernicious anemia, pyloric
10 stenosis, gastritis (bacterial, viral, eosinophilic, stress-induced, chronic erosive, atrophic, plasma cell, and Ménétrier's), and peritoneal diseases (e.g., chyloperitoneum, hemoperitoneum, mesenteric cyst, mesenteric lymphadenitis, mesenteric vascular occlusion, panniculitis, neoplasms, peritonitis, pneumoperitoneum, bubphrenic abscess,).

15 Gastrointestinal disorders also include disorders associated with the small intestine, such as malabsorption syndromes, distension, irritable bowel syndrome, sugar intolerance, celiac disease, duodenal ulcers, duodenitis, tropical sprue, Whipple's disease, intestinal lymphangiectasia, Crohn's disease, appendicitis, obstructions of the ileum, Meckel's diverticulum, multiple diverticula, failure of
20 complete rotation of the small and large intestine, lymphoma, and bacterial and parasitic diseases (such as Traveler's diarrhea, typhoid and paratyphoid, cholera, infection by Roundworms (*Ascariasis lumbricoides*), Hookworms (*Ancylostoma duodenale*), Threadworms (*Enterobius vermicularis*), Tapeworms (*Taenia saginata*, *Echinococcus granulosus*, *Diphyllobothrium spp.*, and *T. solium*).

25 Liver diseases and/or disorders include intrahepatic cholestasis (alagille syndrome, biliary liver cirrhosis), fatty liver (alcoholic fatty liver, reye syndrome), hepatic vein thrombosis, hepatolentricular degeneration, hepatomegaly, hepatopulmonary syndrome, hepatorenal syndrome, portal hypertension (esophageal and gastric varices), liver abscess (amebic liver abscess), liver cirrhosis (alcoholic,
30 biliary and experimental), alcoholic liver diseases (fatty liver, hepatitis, cirrhosis), parasitic (hepatic echinococcosis, fascioliasis, amebic liver abscess), jaundice (hemolytic, hepatocellular, and cholestatic), cholestasis, portal hypertension, liver

enlargement, ascites, hepatitis (alcoholic hepatitis, animal hepatitis, chronic hepatitis (autoimmune, hepatitis B, hepatitis C, hepatitis D, drug induced), toxic hepatitis, viral human hepatitis (hepatitis A, hepatitis B, hepatitis C, hepatitis D, hepatitis E), Wilson's disease, granulomatous hepatitis, secondary biliary cirrhosis, hepatic

5 encephalopathy, portal hypertension, varices, hepatic encephalopathy, primary biliary cirrhosis, primary sclerosing cholangitis, hepatocellular adenoma, hemangiomas, bile stones, liver failure (hepatic encephalopathy, acute liver failure), and liver neoplasms (angiomyolipoma, calcified liver metastases, cystic liver metastases, epithelial

10 tumors, fibrolamellar hepatocarcinoma, focal nodular hyperplasia, hepatic adenoma, hepatobiliary cystadenoma, hepatoblastoma, hepatocellular carcinoma, hepatoma, liver cancer, liver hemangioendothelioma, mesenchymal hamartoma, mesenchymal tumors of liver, nodular regenerative hyperplasia, benign liver tumors (Hepatic cysts [Simple cysts, Polycystic liver disease, Hepatobiliary cystadenoma, Choledochal cyst], Mesenchymal tumors [Mesenchymal hamartoma, Infantile

15 hemangioendothelioma, Hemangioma, Peliosis hepatis, Lipomas, Inflammatory pseudotumor, Miscellaneous], Epithelial tumors [Bile duct epithelium (Bile duct hamartoma, Bile duct adenoma), Hepatocyte (Adenoma, Focal nodular hyperplasia, Nodular regenerative hyperplasia)], malignant liver tumors [hepatocellular, hepatoblastoma, hepatocellular carcinoma, cholangiocellular, cholangiocarcinoma,

20 cystadenocarcinoma, tumors of blood vessels, angiosarcoma, Kaposi's sarcoma, hemangioendothelioma, other tumors, embryonal sarcoma, fibrosarcoma, leiomyosarcoma, rhabdomyosarcoma, carcinosarcoma, teratoma, carcinoid, squamous carcinoma, primary lymphoma]), peliosis hepatis, erythrohepatic porphyria, hepatic porphyria (acute intermittent porphyria, porphyria cutanea tarda), Zellweger

25 syndrome).

Pancreatic diseases and/or disorders include acute pancreatitis, chronic pancreatitis (acute necrotizing pancreatitis, alcoholic pancreatitis), neoplasms (adenocarcinoma of the pancreas, cystadenocarcinoma, insulinoma, gastrinoma, and glucagonoma, cystic neoplasms, islet-cell tumors, pancreoblastoma), and other

30 pancreatic diseases (e.g., cystic fibrosis, cyst (pancreatic pseudocyst, pancreatic fistula, insufficiency)).

Gallbladder diseases include gallstones (cholelithiasis and choledocholithiasis), postcholecystectomy syndrome, diverticulosis of the gallbladder, acute cholecystitis, chronic cholecystitis, bile duct tumors, and mucocele.

Diseases and/or disorders of the large intestine include antibiotic-associated
5 colitis, diverticulitis, ulcerative colitis, acquired megacolon, abscesses, fungal and bacterial infections, anorectal disorders (e.g., fissures, hemorrhoids), colonic diseases (colitis, colonic neoplasms [colon cancer, adenomatous colon polyps (e.g., villous adenoma), colon carcinoma, colorectal cancer], colonic diverticulitis, colonic diverticulosis, megacolon [Hirschsprung disease, toxic megacolon]; sigmoid diseases
10 [proctocolitis, sigmoid neoplasms]), constipation, Crohn's disease, diarrhea (infantile diarrhea, dysentery), duodenal diseases (duodenal neoplasms, duodenal obstruction, duodenal ulcer, duodenitis), enteritis (enterocolitis), HIV enteropathy, ileal diseases (ileal neoplasms, ileitis), immunoproliferative small intestinal disease, inflammatory bowel disease (ulcerative colitis, Crohn's disease), intestinal atresia, parasitic diseases
15 (anisakiasis, balantidiasis, blastocystis infections, cryptosporidiosis, dientamoebiasis, amebic dysentery, giardiasis), intestinal fistula (rectal fistula), intestinal neoplasms (cecal neoplasms, colonic neoplasms, duodenal neoplasms, ileal neoplasms, intestinal polyps, jejunal neoplasms, rectal neoplasms), intestinal obstruction (afferent loop syndrome, duodenal obstruction, impacted feces, intestinal pseudo-obstruction [cecal
20 volvulus], intussusception), intestinal perforation, intestinal polyps (colonic polyps, gardner syndrome, peutz-jeghers syndrome), jejunal diseases (jejunal neoplasms), malabsorption syndromes (blind loop syndrome, celiac disease, lactose intolerance, short bowel syndrome, tropical sprue, whipple's disease), mesenteric vascular occlusion, pneumatosis cystoides intestinalis, protein-losing enteropathies (intestinal
25 lymphangiectasis), rectal diseases (anus diseases, fecal incontinence, hemorrhoids, proctitis, rectal fistula, rectal prolapse, rectocele), peptic ulcer (duodenal ulcer, peptic esophagitis, hemorrhage, perforation, stomach ulcer, Zollinger-Ellison syndrome), postgastrectomy syndromes (dumping syndrome), stomach diseases (e.g., achlorhydria, duodenogastric reflux (bile reflux), gastric antral vascular ectasia,
30 gastric fistula, gastric outlet obstruction, gastritis (atrophic or hypertrophic), gastroparesis, stomach dilatation, stomach diverticulum, stomach neoplasms (gastric cancer, gastric polyps, gastric adenocarcinoma, hyperplastic gastric polyp), stomach

rupture, stomach ulcer, stomach volvulus), tuberculosis, visceroptosis, vomiting (e.g., hematemesis, hyperemesis gravidarum, postoperative nausea and vomiting) and hemorrhagic colitis.

Further diseases and/or disorders of the gastrointestinal system include biliary tract diseases, such as, gastroschisis, fistula (e.g., biliary fistula, esophageal fistula, gastric fistula, intestinal fistula, pancreatic fistula), neoplasms (e.g., biliary tract neoplasms, esophageal neoplasms, such as adenocarcinoma of the esophagus, esophageal squamous cell carcinoma, gastrointestinal neoplasms, pancreatic neoplasms, such as adenocarcinoma of the pancreas, mucinous cystic neoplasm of the pancreas, pancreatic cystic neoplasms, pancreatoblastoma, and peritoneal neoplasms), esophageal disease (e.g., bullous diseases, candidiasis, glycogenic acanthosis, ulceration, barrett esophagus varices, atresia, cyst, diverticulum (e.g., Zenker's diverticulum), fistula (e.g., tracheoesophageal fistula), motility disorders (e.g., CREST syndrome, deglutition disorders, achalasia, spasm, gastroesophageal reflux), neoplasms, perforation (e.g., Boerhaave syndrome, Mallory-Weiss syndrome), stenosis, esophagitis, diaphragmatic hernia (e.g., hiatal hernia); gastrointestinal diseases, such as, gastroenteritis (e.g., cholera morbus, norwalk virus infection), hemorrhage (e.g., hematemesis, melena, peptic ulcer hemorrhage), stomach neoplasms (gastric cancer, gastric polyps, gastric adenocarcinoma, stomach cancer)), hernia (e.g., congenital diaphragmatic hernia, femoral hernia, inguinal hernia, obturator hernia, umbilical hernia, ventral hernia), and intestinal diseases (e.g., cecal diseases (appendicitis, cecal neoplasms)).

Chemotaxis

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may have chemotaxis activity. A chemotaxic molecule attracts or mobilizes cells (e.g., monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells) to a particular site in the body, such as inflammation, infection, or site of hyperproliferation. The mobilized cells can then fight off and/or heal the particular trauma or abnormality.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may increase chemotaxic activity of particular cells. These

chemotactic molecules can then be used to treat inflammation, infection, hyperproliferative disorders, or any immune system disorder by increasing the number of cells targeted to a particular location in the body. For example, chemotactic molecules can be used to treat wounds and other trauma to tissues by attracting immune cells to the injured location. Chemotactic molecules of the present invention can also attract fibroblasts, which can be used to treat wounds.

It is also contemplated that polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may inhibit chemotactic activity. These molecules could also be used to treat disorders. Thus, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention could be used as an inhibitor of chemotaxis.

Binding Activity

A polypeptide of the present invention may be used to screen for molecules that bind to the polypeptide or for molecules to which the polypeptide binds. The binding of the polypeptide and the molecule may activate (agonist), increase, inhibit (antagonist), or decrease activity of the polypeptide or the molecule bound. Examples of such molecules include antibodies, oligonucleotides, proteins (e.g., receptors), or small molecules.

Preferably, the molecule is closely related to the natural ligand of the polypeptide, e.g., a fragment of the ligand, or a natural substrate, a ligand, a structural or functional mimetic. (See, Coligan et al., Current Protocols in Immunology 1(2):Chapter 5 (1991)). Similarly, the molecule can be closely related to the natural receptor to which the polypeptide binds, or at least, a fragment of the receptor capable of being bound by the polypeptide (e.g., active site). In either case, the molecule can be rationally designed using known techniques.

Preferably, the screening for these molecules involves producing appropriate cells which express the polypeptide. Preferred cells include cells from mammals, yeast, *Drosophila*, or *E. coli*. Cells expressing the polypeptide (or cell membrane containing the expressed polypeptide) are then preferably contacted with a test compound potentially containing the molecule to observe binding, stimulation, or inhibition of activity of either the polypeptide or the molecule.

The assay may simply test binding of a candidate compound to the polypeptide, wherein binding is detected by a label, or in an assay involving competition with a labeled competitor. Further, the assay may test whether the candidate compound results in a signal generated by binding to the polypeptide.

5 Alternatively, the assay can be carried out using cell-free preparations, polypeptide/molecule affixed to a solid support, chemical libraries, or natural product mixtures. The assay may also simply comprise the steps of mixing a candidate compound with a solution containing a polypeptide, measuring polypeptide/molecule activity or binding, and comparing the polypeptide/molecule activity or binding to a
10 standard.

Preferably, an ELISA assay can measure polypeptide level or activity in a sample (e.g., biological sample) using a monoclonal or polyclonal antibody. The antibody can measure polypeptide level or activity by either binding, directly or indirectly, to the polypeptide or by competing with the polypeptide for a substrate.

15 Additionally, the receptor to which the polypeptide of the present invention binds can be identified by numerous methods known to those of skill in the art, for example, ligand panning and FACS sorting (Coligan, et al., Current Protocols in Immun., 1(2), Chapter 5, (1991)). For example, expression cloning is employed wherein polyadenylated RNA is prepared from a cell responsive to the polypeptides,
20 for example, NIH3T3 cells which are known to contain multiple receptors for the FGF family proteins, and SC-3 cells, and a cDNA library created from this RNA is divided into pools and used to transfect COS cells or other cells that are not responsive to the polypeptides. Transfected cells which are grown on glass slides are exposed to the polypeptide of the present invention, after they have been labeled. The
25 polypeptides can be labeled by a variety of means including iodination or inclusion of a recognition site for a site-specific protein kinase.

Following fixation and incubation, the slides are subjected to autoradiographic analysis. Positive pools are identified and sub-pools are prepared and re-transfected using an iterative sub-pooling and re-screening process, eventually
30 yielding a single clones that encodes the putative receptor.

As an alternative approach for receptor identification, the labeled polypeptides can be photoaffinity linked with cell membrane or extract preparations that express

the receptor molecule. Cross-linked material is resolved by PAGE analysis and exposed to X-ray film. The labeled complex containing the receptors of the polypeptides can be excised, resolved into peptide fragments, and subjected to protein microsequencing. The amino acid sequence obtained from microsequencing would
5 be used to design a set of degenerate oligonucleotide probes to screen a cDNA library to identify the genes encoding the putative receptors.

Moreover, the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling") may be employed to modulate the activities of the polypeptide of the present invention
10 thereby effectively generating agonists and antagonists of the polypeptide of the present invention. *See generally*, U.S. Patent Nos. 5,605,793, 5,811,238, 5,830,721, 5,834,252, and 5,837,458, and Patten, P. A., *et al.*, *Curr. Opinion Biotechnol.* 8:724-33 (1997); Harayama, S. *Trends Biotechnol.* 16(2):76-82 (1998); Hansson, L. O., *et al.*, *J. Mol. Biol.* 287:265-76 (1999); and Lorenzo, M. M. and Blasco, R.
15 *Biotechniques* 24(2):308-13 (1998); each of these patents and publications are hereby incorporated by reference). In one embodiment, alteration of polynucleotides and corresponding polypeptides may be achieved by DNA shuffling. DNA shuffling involves the assembly of two or more DNA segments into a desired molecule by homologous, or site-specific, recombination. In another embodiment, polynucleotides
20 and corresponding polypeptides may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, one or more components, motifs, sections, parts, domains, fragments, etc., of the polypeptide of the present invention may be recombined with one or more components, motifs, sections, parts, domains,
25 fragments, etc. of one or more heterologous molecules. In preferred embodiments, the heterologous molecules are family members. In further preferred embodiments, the heterologous molecule is a growth factor such as, for example, platelet-derived growth factor (PDGF), insulin-like growth factor (IGF-I), transforming growth factor (TGF)-alpha, epidermal growth factor (EGF), fibroblast growth factor (FGF), TGF-beta, bone morphogenetic protein (BMP)-2, BMP-4, BMP-5, BMP-6, BMP-7,
30 activins A and B, decapentaplegic(dpp), 60A, OP-2, dorsalin, growth differentiation

factors (GDFs), nodal, MIS, inhibin-alpha, TGF-beta1, TGF-beta2, TGF-beta3, TGF-beta5, and glial-derived neurotrophic factor (GDNF).

Other preferred fragments are biologically active fragments of the polypeptide of the present invention. Biologically active fragments are those exhibiting activity
5 similar, but not necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

Additionally, this invention provides a method of screening compounds to identify those which modulate the action of the polypeptide of the present invention.
10 An example of such an assay comprises combining a mammalian fibroblast cell, a the polypeptide of the present invention, the compound to be screened and $^3\text{[H]}$ thymidine under cell culture conditions where the fibroblast cell would normally proliferate. A control assay may be performed in the absence of the compound to be screened and compared to the amount of fibroblast proliferation in the presence of the
15 compound to determine if the compound stimulates proliferation by determining the uptake of $^3\text{[H]}$ thymidine in each case. The amount of fibroblast cell proliferation is measured by liquid scintillation chromatography which measures the incorporation of $^3\text{[H]}$ thymidine. Both agonist and antagonist compounds may be identified by this procedure.

20 In another method, a mammalian cell or membrane preparation expressing a receptor for a polypeptide of the present invention is incubated with a labeled polypeptide of the present invention in the presence of the compound. The ability of the compound to enhance or block this interaction could then be measured. Alternatively, the response of a known second messenger system following
25 interaction of a compound to be screened and the receptor is measured and the ability of the compound to bind to the receptor and elicit a second messenger response is measured to determine if the compound is a potential agonist or antagonist. Such second messenger systems include but are not limited to, cAMP guanylate cyclase, ion channels or phosphoinositide hydrolysis.

30 All of these above assays can be used as diagnostic or prognostic markers. The molecules discovered using these assays can be used to treat disease or to bring

about a particular result in a patient (e.g., blood vessel growth) by activating or inhibiting the polypeptide/molecule. Moreover, the assays can discover agents which may inhibit or enhance the production of the polypeptides of the invention from suitably manipulated cells or tissues.

- 5 Therefore, the invention includes a method of identifying compounds which bind to a polypeptide of the invention comprising the steps of: (a) incubating a candidate binding compound with a polypeptide of the present invention; and (b) determining if binding has occurred. Moreover, the invention includes a method of identifying agonists/antagonists comprising the steps of: (a) incubating a candidate
- 10 compound with a polypeptide of the present invention, (b) assaying a biological activity, and (b) determining if a biological activity of the polypeptide has been altered.

Targeted Delivery

- 15 In another embodiment, the invention provides a method of delivering compositions to targeted cells expressing a receptor for a polypeptide of the invention, or cells expressing a cell bound form of a polypeptide of the invention.

- As discussed herein, polypeptides or antibodies of the invention may be associated with heterologous polypeptides, heterologous nucleic acids, toxins, or
- 20 prodrugs via hydrophobic, hydrophilic, ionic and/or covalent interactions. In one embodiment, the invention provides a method for the specific delivery of compositions of the invention to cells by administering polypeptides of the invention (including antibodies) that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method for delivering a therapeutic
- 25 protein into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

- In another embodiment, the invention provides a method for the specific
- 30 destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention (e.g., polypeptides of the invention or antibodies of the invention) in association with toxins or cytotoxic prodrugs.

By "toxin" is meant compounds that bind and activate endogenous cytotoxic effector systems, radioisotopes, holotoxins, modified toxins, catalytic subunits of toxins, or any molecules or enzymes not normally present in or on the surface of a cell that under defined conditions cause the cell's death. Toxins that may be used according to the methods of the invention include, but are not limited to, radioisotopes known in the art, compounds such as, for example, antibodies (or complement fixing containing portions thereof) that bind an inherent or induced endogenous cytotoxic effector system, thymidine kinase, endonuclease, RNase, alpha toxin, ricin, abrin, *Pseudomonas* exotoxin A, diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin. By "cytotoxic prodrug" is meant a non-toxic compound that is converted by an enzyme, normally present in the cell, into a cytotoxic compound. Cytotoxic prodrugs that may be used according to the methods of the invention include, but are not limited to, glutamyl derivatives of benzoic acid mustard alkylating agent, phosphate derivatives of etoposide or mitomycin C, cytosine arabinoside, daunorubisin, and phenoxyacetamide derivatives of doxorubicin.

Drug Screening

Further contemplated is the use of the polypeptides of the present invention, or the polynucleotides encoding these polypeptides, to screen for molecules which modify the activities of the polypeptides of the present invention. Such a method would include contacting the polypeptide of the present invention with a selected compound(s) suspected of having antagonist or agonist activity, and assaying the activity of these polypeptides following binding.

This invention is particularly useful for screening therapeutic compounds by using the polypeptides of the present invention, or binding fragments thereof, in any of a variety of drug screening techniques. The polypeptide or fragment employed in such a test may be affixed to a solid support, expressed on a cell surface, free in solution, or located intracellularly. One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant nucleic acids expressing the polypeptide or fragment. Drugs are screened against such transformed cells in competitive binding assays. One may measure, for example, the formulation

of complexes between the agent being tested and a polypeptide of the present invention.

Thus, the present invention provides methods of screening for drugs or any other agents which affect activities mediated by the polypeptides of the present invention. These methods comprise contacting such an agent with a polypeptide of the present invention or a fragment thereof and assaying for the presence of a complex between the agent and the polypeptide or a fragment thereof, by methods well known in the art. In such a competitive binding assay, the agents to screen are typically labeled. Following incubation, free agent is separated from that present in bound form, and the amount of free or uncomplexed label is a measure of the ability of a particular agent to bind to the polypeptides of the present invention.

Another technique for drug screening provides high throughput screening for compounds having suitable binding affinity to the polypeptides of the present invention, and is described in great detail in European Patent Application 84/03564, published on September 13, 1984, which is incorporated herein by reference herein. Briefly stated, large numbers of different small peptide test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. The peptide test compounds are reacted with polypeptides of the present invention and washed. Bound polypeptides are then detected by methods well known in the art. Purified polypeptides are coated directly onto plates for use in the aforementioned drug screening techniques. In addition, non-neutralizing antibodies may be used to capture the peptide and immobilize it on the solid support.

This invention also contemplates the use of competitive drug screening assays in which neutralizing antibodies capable of binding polypeptides of the present invention specifically compete with a test compound for binding to the polypeptides or fragments thereof. In this manner, the antibodies are used to detect the presence of any peptide which shares one or more antigenic epitopes with a polypeptide of the invention.

30 **Polypeptides of the Invention Binding Peptides and Other Molecules**

The invention also encompasses screening methods for identifying polypeptides and nonpolypeptides that bind polypeptides of the invention, and the

polypeptide of the invention binding molecules identified thereby. These binding molecules are useful, for example, as agonists and antagonists of the polypeptides of the invention. Such agonists and antagonists can be used, in accordance with the invention, in the therapeutic embodiments described in detail, below.

5 This method comprises the steps of: contacting a polypeptide of the invention with a plurality of molecules; and identifying a molecule that binds the polypeptide of the invention.

 The step of contacting the polypeptide of the invention with the plurality of molecules may be effected in a number of ways. For example, one may contemplate
10 immobilizing the polypeptide of the invention on a solid support and bringing a solution of the plurality of molecules in contact with the immobilized polypeptide of the invention. Such a procedure would be akin to an affinity chromatographic process, with the affinity matrix being comprised of the immobilized polypeptide of the invention. The molecules having a selective affinity for the polypeptide of the
15 invention can then be purified by affinity selection. The nature of the solid support, process for attachment of the polypeptide of the invention to the solid support, solvent, and conditions of the affinity isolation or selection are largely conventional and well known to those of ordinary skill in the art.

 Alternatively, one may also separate a plurality of polypeptides into
20 substantially separate fractions comprising a subset of or individual polypeptides. For instance, one can separate the plurality of polypeptides by gel electrophoresis, column chromatography, or like method known to those of ordinary skill for the separation of polypeptides. The individual polypeptides can also be produced by a transformed host cell in such a way as to be expressed on or about its outer surface (e.g., a recombinant
25 phage). Individual isolates can then be "probed" by the polypeptide of the invention, optionally in the presence of an inducer should one be required for expression, to determine if any selective affinity interaction takes place between the polypeptide of the invention and the individual clone. Prior to contacting the polypeptide of the invention with each fraction comprising individual polypeptides, the polypeptides
30 could first be transferred to a solid support for additional convenience. Such a solid support may simply be a piece of filter membrane, such as one made of nitrocellulose or nylon. In this manner, positive clones could be identified from a collection of

transformed host cells of an expression library, which harbor a DNA construct encoding a polypeptide having a selective affinity for a polypeptide of the invention. Furthermore, the amino acid sequence of the polypeptide having a selective affinity for the polypeptide of the invention can be determined directly by conventional means or the coding sequence of the DNA encoding the polypeptide can frequently be determined more conveniently. The primary sequence can then be deduced from the corresponding DNA sequence. If the amino acid sequence is to be determined from the polypeptide itself, one may use microsequencing techniques. The sequencing technique may include mass spectroscopy.

In certain situations, it may be desirable to wash away any unbound polypeptide of the invention, or alternatively, unbound polypeptides, from a mixture of the polypeptide of the invention and the plurality of polypeptides prior to attempting to determine or to detect the presence of a selective affinity interaction. Such a wash step may be particularly desirable when the polypeptide of the invention or the plurality of polypeptides is bound to a solid support.

The plurality of molecules provided according to this method may be provided by way of diversity libraries, such as random or combinatorial peptide or nonpeptide libraries which can be screened for molecules that specifically bind to a polypeptide of the invention. Many libraries are known in the art that can be used, e.g., chemically synthesized libraries, recombinant (e.g., phage display libraries), and in vitro translation-based libraries. Examples of chemically synthesized libraries are described in Fodor et al., 1991, *Science* 251:767-773; Houghten et al., 1991, *Nature* 354:84-86; Lam et al., 1991, *Nature* 354:82-84; Medynski, 1994, *Bio/Technology* 12:709-710; Gallop et al., 1994, *J. Medicinal Chemistry* 37(9):1233-1251; Ohlmeyer et al., 1993, *Proc. Natl. Acad. Sci. USA* 90:10922-10926; Erb et al., 1994, *Proc. Natl. Acad. Sci. USA* 91:11422-11426; Houghten et al., 1992, *Biotechniques* 13:412; Jayawickreme et al., 1994, *Proc. Natl. Acad. Sci. USA* 91:1614-1618; Salmon et al., 1993, *Proc. Natl. Acad. Sci. USA* 90:11708-11712; PCT Publication No. WO 93/20242; and Brenner and Lerner, 1992, *Proc. Natl. Acad. Sci. USA* 89:5381-5383.

Examples of phage display libraries are described in Scott and Smith, 1990, *Science* 249:386-390; Devlin et al., 1990, *Science*, 249:404-406; Christian, R. B., et al., 1992, *J. Mol. Biol.* 227:711-718; Lenstra, 1992, *J. Immunol. Meth.* 152:149-157;

Kay et al., 1993, Gene 128:59-65; and PCT Publication No. WO 94/18318 dated Aug. 18, 1994.

In vitro translation-based libraries include but are not limited to those described in PCT Publication No. WO 91/05058 dated Apr. 18, 1991; and Mattheakis
5 et al., 1994, Proc. Natl. Acad. Sci. USA 91:9022-9026.

By way of examples of nonpeptide libraries, a benzodiazepine library (see e.g., Bunin et al., 1994, Proc. Natl. Acad. Sci. USA 91:4708-4712) can be adapted for use. Peptoid libraries (Simon et al., 1992, Proc. Natl. Acad. Sci. USA 89:9367-9371) can also be used. Another example of a library that can be used, in which the amide
10 functionalities in peptides have been permethylated to generate a chemically transformed combinatorial library, is described by Ostresh et al. (1994, Proc. Natl. Acad. Sci. USA 91:11138-11142).

The variety of non-peptide libraries that are useful in the present invention is great. For example, Ecker and Crooke, 1995, Bio/Technology 13:351-360 list
15 benzodiazepines, hydantoins, piperazinediones, biphenyls; sugar analogs, beta-mercaptoketones, arylacetic acids, acylpiperidines, benzopyrans, cubanes, xanthines, aminimides, and oxazolones as among the chemical species that form the basis of various libraries.

Non-peptide libraries can be classified broadly into two types: decorated
20 monomers and oligomers. Decorated monomer libraries employ a relatively simple scaffold structure upon which a variety functional groups is added. Often the scaffold will be a molecule with a known useful pharmacological activity. For example, the scaffold might be the benzodiazepine structure.

Non-peptide oligomer libraries utilize a large number of monomers that are
25 assembled together in ways that create new shapes that depend on the order of the monomers. Among the monomer units that have been used are carbamates, pyrrolinones, and morpholinos. Peptoids, peptide-like oligomers in which the side chain is attached to the alpha amino group rather than the alpha carbon, form the basis of another version of non-peptide oligomer libraries. The first non-peptide oligomer
30 libraries utilized a single type of monomer and thus contained a repeating backbone. Recent libraries have utilized more than one monomer, giving the libraries added flexibility.

Screening the libraries can be accomplished by any of a variety of commonly known methods. See, e.g., the following references, which disclose screening of peptide libraries: Parmley and Smith, 1989, *Adv. Exp. Med. Biol.* 251:215-218; Scott and Smith, 1990, *Science* 249:386-390; Fowlkes et al., 1992, *BioTechniques* 13:422-427; Oldenburg et al., 1992, *Proc. Natl. Acad. Sci. USA* 89:5393-5397; Yu et al., 1994, *Cell* 76:933-945; Staudt et al., 1988, *Science* 241:577-580; Bock et al., 1992, *Nature* 355:564-566; Tuerk et al., 1992, *Proc. Natl. Acad. Sci. USA* 89:6988-6992; Ellington et al., 1992, *Nature* 355:850-852; U.S. Pat. No. 5,096,815, U.S. Pat. No. 5,223,409, and U.S. Pat. No. 5,198,346, all to Ladner et al.; Rebar and Pabo, 1993, *Science* 263:671-673; and CT Publication No. WO 94/18318.

In a specific embodiment, screening to identify a molecule that binds a polypeptide of the invention can be carried out by contacting the library members with a polypeptide of the invention immobilized on a solid phase and harvesting those library members that bind to the polypeptide of the invention. Examples of such screening methods, termed "panning" techniques are described by way of example in Parmley and Smith, 1988, *Gene* 73:305-318; Fowlkes et al., 1992, *BioTechniques* 13:422-427; PCT Publication No. WO 94/18318; and in references cited herein.

In another embodiment, the two-hybrid system for selecting interacting proteins in yeast (Fields and Song, 1989, *Nature* 340:245-246; Chien et al., 1991, *Proc. Natl. Acad. Sci. USA* 88:9578-9582) can be used to identify molecules that specifically bind to a polypeptide of the invention.

Where the polypeptide of the invention binding molecule is a polypeptide, the polypeptide can be conveniently selected from any peptide library, including random peptide libraries, combinatorial peptide libraries, or biased peptide libraries. The term "biased" is used herein to mean that the method of generating the library is manipulated so as to restrict one or more parameters that govern the diversity of the resulting collection of molecules, in this case peptides.

Thus, a truly random peptide library would generate a collection of peptides in which the probability of finding a particular amino acid at a given position of the peptide is the same for all 20 amino acids. A bias can be introduced into the library, however, by specifying, for example, that a lysine occur every fifth amino acid or that positions 4, 8, and 9 of a decapeptide library be fixed to include only arginine.

Clearly, many types of biases can be contemplated, and the present invention is not restricted to any particular bias. Furthermore, the present invention contemplates specific types of peptide libraries, such as phage displayed peptide libraries and those that utilize a DNA construct comprising a lambda phage vector with a DNA insert.

5 As mentioned above, in the case of a polypeptide of the invention binding molecule that is a polypeptide, the polypeptide may have about 6 to less than about 60 amino acid residues, preferably about 6 to about 10 amino acid residues, and most preferably, about 6 to about 22 amino acids. In another embodiment, a polypeptide of the invention binding polypeptide has in the range of 15-100 amino acids, or 20-50
10 amino acids.

The selected polypeptide of the invention binding polypeptide can be obtained by chemical synthesis or recombinant expression.

Antisense And Ribozyme (Antagonists)

15 In specific embodiments, antagonists according to the present invention are nucleic acids corresponding to the sequences contained in SEQ ID NO:X, or the complementary strand thereof, and/or to nucleotide sequences contained a deposited clone. In one embodiment, antisense sequence is generated internally by the organism, in another embodiment, the antisense sequence is separately administered
20 (see, for example, O'Connor, Neurochem., 56:560 (1991). Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Antisense technology can be used to control gene expression through antisense DNA or RNA, or through triple-helix formation. Antisense techniques are discussed for example, in Okano, Neurochem., 56:560 (1991); Oligodeoxynucleotides as Antisense
25 Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Triple helix formation is discussed in, for instance, Lee et al., Nucleic Acids Research, 6:3073 (1979); Cooney et al., Science, 241:456 (1988); and Dervan et al., Science, 251:1300 (1991). The methods are based on binding of a polynucleotide to a complementary DNA or RNA.

30 For example, the use of c-myc and c-myb antisense RNA constructs to inhibit the growth of the non-lymphocytic leukemia cell line HL-60 and other cell lines was previously described. (Wickstrom et al. (1988); Anfossi et al. (1989)). These

experiments were performed in vitro by incubating cells with the oligoribonucleotide. A similar procedure for in vivo use is described in WO 91/15580. Briefly, a pair of oligonucleotides for a given antisense RNA is produced as follows: A sequence complimentary to the first 15 bases of the open reading frame is flanked by an EcoR1 site on the 5' end and a HindIII site on the 3' end. Next, the pair of oligonucleotides is heated at 90°C for one minute and then annealed in 2X ligation buffer (20mM TRIS HCl pH 7.5, 10mM MgCl₂, 10mM dithiothreitol (DTT) and 0.2 mM ATP) and then ligated to the EcoR1/Hind III site of the retroviral vector PMV7 (WO 91/15580).

For example, the 5' coding portion of a polynucleotide that encodes the mature polypeptide of the present invention may be used to design an antisense RNA oligonucleotide of from about 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription thereby preventing transcription and the production of the receptor. The antisense RNA oligonucleotide hybridizes to the mRNA in vivo and blocks translation of the mRNA molecule into receptor polypeptide.

In one embodiment, the antisense nucleic acid of the invention is produced intracellularly by transcription from an exogenous sequence. For example, a vector or a portion thereof, is transcribed, producing an antisense nucleic acid (RNA) of the invention. Such a vector would contain a sequence encoding the antisense nucleic acid of the invention. Such a vector can remain episomal or become chromosomally integrated, as long as it can be transcribed to produce the desired antisense RNA. Such vectors can be constructed by recombinant DNA technology methods standard in the art. Vectors can be plasmid, viral, or others known in the art, used for replication and expression in vertebrate cells. Expression of the sequence encoding a polypeptide of the invention, or fragments thereof, can be by any promoter known in the art to act in vertebrate, preferably human cells. Such promoters can be inducible or constitutive. Such promoters include, but are not limited to, the SV40 early promoter region (Bernoist and Chambon, *Nature*, 29:304-310 (1981), the promoter contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto et al., *Cell*, 22:787-797 (1980), the herpes thymidine promoter (Wagner et al., *Proc. Natl. Acad. Sci. U.S.A.*, 78:1441-1445 (1981), the regulatory sequences of the metallothionein gene (Brinster et al., *Nature*, 296:39-42 (1982)), etc.

The antisense nucleic acids of the invention comprise a sequence complementary to at least a portion of an RNA transcript of a gene of interest. However, absolute complementarity, although preferred, is not required. A sequence “complementary to at least a portion of an RNA,” referred to herein, means a
5 sequence having sufficient complementarity to be able to hybridize with the RNA, forming a stable duplex; in the case of double stranded antisense nucleic acids of the invention, a single strand of the duplex DNA may thus be tested, or triplex formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the antisense nucleic acid. Generally, the larger the
10 hybridizing nucleic acid, the more base mismatches with a RNA sequence of the invention it may contain and still form a stable duplex (or triplex as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of standard procedures to determine the melting point of the hybridized complex.

Oligonucleotides that are complementary to the 5′ end of the message, *e.g.*,
15 the 5′ untranslated sequence up to and including the AUG initiation codon, should work most efficiently at inhibiting translation. However, sequences complementary to the 3′ untranslated sequences of mRNAs have been shown to be effective at inhibiting translation of mRNAs as well. See generally, Wagner, R., *Nature*, 372:333-335 (1994). Thus, oligonucleotides complementary to either the 5′ - or 3′ -
20 non- translated, non-coding regions of a polynucleotide sequence of the invention could be used in an antisense approach to inhibit translation of endogenous mRNA. Oligonucleotides complementary to the 5′ untranslated region of the mRNA should include the complement of the AUG start codon. Antisense oligonucleotides complementary to mRNA coding regions are less efficient inhibitors of translation but
25 could be used in accordance with the invention. Whether designed to hybridize to the 5′ -, 3′ - or coding region of mRNA, antisense nucleic acids should be at least six nucleotides in length, and are preferably oligonucleotides ranging from 6 to about 50 nucleotides in length. In specific aspects the oligonucleotide is at least 10 nucleotides, at least 17 nucleotides, at least 25 nucleotides or at least 50 nucleotides.

30 The polynucleotides of the invention can be DNA or RNA or chimeric mixtures or derivatives or modified versions thereof, single-stranded or double-stranded. The oligonucleotide can be modified at the base moiety, sugar moiety, or

phosphate backbone, for example, to improve stability of the molecule, hybridization, etc. The oligonucleotide may include other appended groups such as peptides (e.g., for targeting host cell receptors in vivo), or agents facilitating transport across the cell membrane (see, e.g., Letsinger et al., Proc. Natl. Acad. Sci. U.S.A. 86:6553-6556 (1989); Lemaitre et al., Proc. Natl. Acad. Sci., 84:648-652 (1987); PCT Publication NO: WO88/09810, published December 15, 1988) or the blood-brain barrier (see, e.g., PCT Publication NO: WO89/10134, published April 25, 1988), hybridization-triggered cleavage agents. (See, e.g., Krol et al., BioTechniques, 6:958-976 (1988)) or intercalating agents. (See, e.g., Zon, Pharm. Res., 5:539-549 (1988)). To this end, the oligonucleotide may be conjugated to another molecule, e.g., a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

The antisense oligonucleotide may comprise at least one modified base moiety which is selected from the group including, but not limited to, 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxymethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine.

The antisense oligonucleotide may also comprise at least one modified sugar moiety selected from the group including, but not limited to, arabinose, 2-fluoroarabinose, xylulose, and hexose.

In yet another embodiment, the antisense oligonucleotide comprises at least one modified phosphate backbone selected from the group including, but not limited

to, a phosphorothioate, a phosphorodithioate, a phosphoramidothioate, a phosphoramidate, a phosphordiamidate, a methylphosphonate, an alkyl phosphotriester, and a formacetal or analog thereof.

In yet another embodiment, the antisense oligonucleotide is an a-anomeric oligonucleotide. An a-anomeric oligonucleotide forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual b-units, the strands run parallel to each other (Gautier et al., Nucl. Acids Res., 15:6625-6641 (1987)). The oligonucleotide is a 2-O-methylribonucleotide (Inoue et al., Nucl. Acids Res., 15:6131-6148 (1987)), or a chimeric RNA-DNA analogue (Inoue et al., FEBS Lett. 10 215:327-330 (1987)).

Polynucleotides of the invention may be synthesized by standard methods known in the art, e.g. by use of an automated DNA synthesizer (such as are commercially available from Biosearch, Applied Biosystems, etc.). As examples, phosphorothioate oligonucleotides may be synthesized by the method of Stein et al. 15 (Nucl. Acids Res., 16:3209 (1988)), methylphosphonate oligonucleotides can be prepared by use of controlled pore glass polymer supports (Sarin et al., Proc. Natl. Acad. Sci. U.S.A., 85:7448-7451 (1988)), etc.

While antisense nucleotides complementary to the coding region sequence of the invention could be used, those complementary to the transcribed untranslated 20 region are most preferred.

Potential antagonists according to the invention also include catalytic RNA, or a ribozyme (See, e.g., PCT International Publication WO 90/11364, published October 4, 1990; Sarver et al, Science, 247:1222-1225 (1990). While ribozymes that cleave mRNA at site specific recognition sequences can be used to destroy mRNAs 25 corresponding to the polynucleotides of the invention, the use of hammerhead ribozymes is preferred. Hammerhead ribozymes cleave mRNAs at locations dictated by flanking regions that form complementary base pairs with the target mRNA. The sole requirement is that the target mRNA have the following sequence of two bases: 5' -UG-3'. The construction and production of hammerhead ribozymes is well 30 known in the art and is described more fully in Haseloff and Gerlach, Nature, 334:585-591 (1988). There are numerous potential hammerhead ribozyme cleavage sites within each nucleotide sequence disclosed in the sequence listing. Preferably,

the ribozyme is engineered so that the cleavage recognition site is located near the 5' end of the mRNA corresponding to the polynucleotides of the invention; i.e., to increase efficiency and minimize the intracellular accumulation of non-functional mRNA transcripts.

5 As in the antisense approach, the ribozymes of the invention can be composed of modified oligonucleotides (e.g. for improved stability, targeting, etc.) and should be delivered to cells which express the polynucleotides of the invention in vivo. DNA constructs encoding the ribozyme may be introduced into the cell in the same manner as described above for the introduction of antisense encoding DNA. A
10 preferred method of delivery involves using a DNA construct "encoding" the ribozyme under the control of a strong constitutive promoter, such as, for example, pol III or pol II promoter, so that transfected cells will produce sufficient quantities of the ribozyme to destroy endogenous messages and inhibit translation. Since ribozymes unlike antisense molecules, are catalytic, a lower intracellular
15 concentration is required for efficiency.

 Antagonist/agonist compounds may be employed to inhibit the cell growth and proliferation effects of the polypeptides of the present invention on neoplastic cells and tissues, i.e. stimulation of angiogenesis of tumors, and, therefore, retard or prevent abnormal cellular growth and proliferation, for example, in tumor formation
20 or growth.

 The antagonist/agonist may also be employed to prevent hyper-vascular diseases, and prevent the proliferation of epithelial lens cells after extracapsular cataract surgery. Prevention of the mitogenic activity of the polypeptides of the present invention may also be desirable in cases such as restenosis after balloon
25 angioplasty.

 The antagonist/agonist may also be employed to prevent the growth of scar tissue during wound healing.

 The antagonist/agonist may also be employed to treat, prevent, and/or diagnose the diseases described herein.

30 Thus, the invention provides a method of treating or preventing diseases, disorders, and/or conditions, including but not limited to the diseases, disorders, and/or conditions listed throughout this application, associated with overexpression of

a polynucleotide of the present invention by administering to a patient (a) an antisense molecule directed to the polynucleotide of the present invention, and/or (b) a ribozyme directed to the polynucleotide of the present invention.

invention, and/or (b) a ribozyme directed to the polynucleotide of the present
5 invention

Other Activities

The polypeptide of the present invention, as a result of the ability to stimulate vascular endothelial cell growth, may be employed in treatment for stimulating re-vascularization of ischemic tissues due to various disease conditions such as
10 thrombosis, arteriosclerosis, and other cardiovascular conditions. These polypeptide may also be employed to stimulate angiogenesis and limb regeneration, as discussed above.

The polypeptide may also be employed for treating wounds due to injuries, burns, post-operative tissue repair, and ulcers since they are mitogenic to various cells
15 of different origins, such as fibroblast cells and skeletal muscle cells, and therefore, facilitate the repair or replacement of damaged or diseased tissue.

The polypeptide of the present invention may also be employed stimulate neuronal growth and to treat, prevent, and/or diagnose neuronal damage which occurs
20 in certain neuronal disorders or neuro-degenerative conditions such as Alzheimer's disease, Parkinson's disease, and AIDS-related complex. The polypeptide of the invention may have the ability to stimulate chondrocyte growth, therefore, they may be employed to enhance bone and periodontal regeneration and aid in tissue transplants or bone grafts.

25 The polypeptide of the present invention may be also be employed to prevent skin aging due to sunburn by stimulating keratinocyte growth.

The polypeptide of the invention may also be employed for preventing hair loss, since FGF family members activate hair-forming cells and promotes melanocyte growth. Along the same lines, the polypeptides of the present invention may be
30 employed to stimulate growth and differentiation of hematopoietic cells and bone marrow cells when used in combination with other cytokines.

The polypeptide of the invention may also be employed to maintain organs before transplantation or for supporting cell culture of primary tissues.

The polypeptide of the present invention may also be employed for inducing tissue of mesodermal origin to differentiate in early embryos.

5 The polypeptide or polynucleotides and/or agonist or antagonists of the present invention may also increase or decrease the differentiation or proliferation of embryonic stem cells, besides, as discussed above, hematopoietic lineage.

10 The polypeptide or polynucleotides and/or agonist or antagonists of the present invention may also be used to modulate mammalian characteristics, such as body height, weight, hair color, eye color, skin, percentage of adipose tissue, pigmentation, size, and shape (e.g., cosmetic surgery). Similarly, polypeptides or polynucleotides and/or agonist or antagonists of the present invention may be used to modulate mammalian metabolism affecting catabolism, anabolism, processing, utilization, and storage of energy.

15 A polypeptide, polynucleotide, agonist, or antagonist of the present invention may be used to treat weight disorders, including but not limited to, obesity, cachexia, wasting disease, anorexia, and bulimia.

20 Polypeptide or polynucleotides and/or agonist or antagonists of the present invention may be used to change a mammal's mental state or physical state by influencing biorhythms, cardiac rhythms, depression (including depressive diseases, disorders, and/or conditions), tendency for violence, tolerance for pain, reproductive capabilities (preferably by Activin or Inhibin-like activity), hormonal or endocrine levels, appetite, libido, memory, stress, or other cognitive qualities.

25 Polypeptide or polynucleotides and/or agonist or antagonists of the present invention may also be used as a food additive or preservative, such as to increase or decrease storage capabilities, fat content, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional components.

Other Preferred Embodiments

30 Other preferred embodiments of the claimed invention include an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95%

identical to a sequence of at least about 50 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1A.

Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of
5 positions beginning with the nucleotide at about the position of the 5' Nucleotide of the Clone Sequence and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1A.

Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of
10 positions beginning with the nucleotide at about the position of the 5' Nucleotide of the Start Codon and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1A.

Similarly preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the
15 range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the First Amino Acid of the Signal Peptide and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1A.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide
20 sequence which is at least 95% identical to a sequence of at least about 150 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X.

Further preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 500 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X.

25 A further preferred embodiment is a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the nucleotide sequence of SEQ ID NO:X beginning with the nucleotide at about the position of the 5' Nucleotide of the First Amino Acid of the Signal Peptide and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X
30 in Table 1A.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence of SEQ ID NO:X.

Also preferred is an isolated nucleic acid molecule which hybridizes under
5 stringent hybridization conditions to a nucleic acid molecule, wherein said nucleic acid molecule which hybridizes does not hybridize under stringent hybridization conditions to a nucleic acid molecule having a nucleotide sequence consisting of only A residues or of only T residues.

Also preferred is a composition of matter comprising a DNA molecule which
10 comprises a human cDNA clone identified by a cDNA Clone Identifier in Table 1A, which DNA molecule is contained in the material deposited with the American Type Culture Collection and given the ATCC Deposit Number shown in Table 1A for said cDNA Clone Identifier.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide
15 sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in the nucleotide sequence of a human cDNA clone identified by a cDNA Clone Identifier in Table 1A, which DNA molecule is contained in the deposit given the ATCC Deposit Number shown in Table 1A.

Also preferred is an isolated nucleic acid molecule, wherein said sequence of
20 at least 50 contiguous nucleotides is included in the nucleotide sequence of the complete open reading frame sequence encoded by said human cDNA clone.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 150 contiguous nucleotides in the nucleotide sequence encoded by said human cDNA clone.

25 A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 500 contiguous nucleotides in the nucleotide sequence encoded by said human cDNA clone.

A further preferred embodiment is an isolated nucleic acid molecule
30 comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence encoded by said human cDNA clone.

A further preferred embodiment is a method for detecting in a biological sample a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1A; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1A and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1A; which method comprises a step of comparing a nucleotide sequence of at least one nucleic acid molecule in said sample with a sequence selected from said group and determining whether the sequence of said nucleic acid molecule in said sample is at least 95% identical to said selected sequence.

Also preferred is the above method wherein said step of comparing sequences comprises determining the extent of nucleic acid hybridization between nucleic acid molecules in said sample and a nucleic acid molecule comprising said sequence selected from said group. Similarly, also preferred is the above method wherein said step of comparing sequences is performed by comparing the nucleotide sequence determined from a nucleic acid molecule in said sample with said sequence selected from said group. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

A further preferred embodiment is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting nucleic acid molecules in said sample, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1A; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1A and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1A.

The method for identifying the species, tissue or cell type of a biological sample can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least

one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a gene encoding a secreted protein identified in Table 1A, which method comprises a step of detecting in a biological sample obtained from said subject nucleic acid molecules, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1A; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1A and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1A.

The method for diagnosing a pathological condition can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Also preferred is a composition of matter comprising isolated nucleic acid molecules wherein the nucleotide sequences of said nucleic acid molecules comprise a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1A; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1A and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1A. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1A.

Also preferred is a polypeptide, wherein said sequence of contiguous amino acids is included in the amino acid sequence of SEQ ID NO:Y in the range of positions beginning with the residue at about the position of the First Amino Acid of the Secreted Portion and ending with the residue at about the Last Amino Acid of the Open Reading Frame as set forth for SEQ ID NO:Y in Table 1A.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the complete amino acid sequence of SEQ ID NO:Y.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1A and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1A.

Also preferred is a polypeptide wherein said sequence of contiguous amino acids is included in the amino acid sequence of a secreted portion of the secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1A and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1A.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1A and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1A.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of the secreted portion of the protein encoded by a human

cDNA clone identified by a cDNA Clone Identifier in Table 1A and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1A.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1A and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1A.

Further preferred is an isolated antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1A; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1A and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1A.

Further preferred is a method for detecting in a biological sample a polypeptide comprising an amino acid sequence which is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1A; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1A and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1A; which method comprises a step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group and determining whether the sequence of said polypeptide molecule in said sample is at least 90% identical to said sequence of at least 10 contiguous amino acids.

Also preferred is the above method wherein said step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group comprises determining the extent of specific binding of polypeptides in said sample to an antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of:

an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1A; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1A and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1A.

5 Also preferred is the above method wherein said step of comparing sequences is performed by comparing the amino acid sequence determined from a polypeptide molecule in said sample with said sequence selected from said group.

Also preferred is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting polypeptide molecules
10 in said sample, if any, comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1A; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in
15 Table 1A and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1A.

Also preferred is the above method for identifying the species, tissue or cell type of a biological sample, which method comprises a step of detecting polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid
20 sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the above group.

Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a gene encoding a secreted
25 protein identified in Table 1A, which method comprises a step of detecting in a biological sample obtained from said subject polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino
30 acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1A; and a complete amino acid sequence of a secreted protein encoded by a human cDNA

clone identified by a cDNA Clone Identifier in Table 1A and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1A.

In any of these methods, the step of detecting said polypeptide molecules includes using an antibody.

- 5 Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a nucleotide sequence encoding a polypeptide wherein said polypeptide comprises an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y
- 10 wherein Y is any integer as defined in Table 1A; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1A and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1A.

- Also preferred is an isolated nucleic acid molecule, wherein said nucleotide
- 15 sequence encoding a polypeptide has been optimized for expression of said polypeptide in a prokaryotic host.

- Also preferred is an isolated nucleic acid molecule, wherein said polypeptide comprises an amino acid sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1A; and
- 20 a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1A and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1A.

- Further preferred is a method of making a recombinant vector comprising inserting any of the above isolated nucleic acid molecule into a vector. Also preferred
- 25 is the recombinant vector produced by this method. Also preferred is a method of making a recombinant host cell comprising introducing the vector into a host cell, as well as the recombinant host cell produced by this method.

- Also preferred is a method of making an isolated polypeptide comprising culturing this recombinant host cell under conditions such that said polypeptide is
- 30 expressed and recovering said polypeptide. Also preferred is this method of making an isolated polypeptide, wherein said recombinant host cell is a eukaryotic cell and said polypeptide is a secreted portion of a human secreted protein comprising an

amino acid sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y beginning with the residue at the position of the First Amino Acid of the Secreted Portion of SEQ ID NO:Y wherein Y is an integer set forth in Table 1A and said position of the First Amino Acid of the Secreted Portion of SEQ ID NO:Y is defined in Table 1A; and an amino acid sequence of a secreted portion of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1A and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1A. The isolated polypeptide produced by this method is also preferred.

Also preferred is a method of treatment of an individual in need of an increased level of a secreted protein activity, which method comprises administering to such an individual a pharmaceutical composition comprising an amount of an isolated polypeptide, polynucleotide, or antibody of the claimed invention effective to increase the level of said protein activity in said individual.

The above-recited applications have uses in a wide variety of hosts. Such hosts include, but are not limited to, human, murine, rabbit, goat, guinea pig, camel, horse, mouse, rat, hamster, pig, micro-pig, chicken, goat, cow, sheep, dog, cat, non-human primate, and human. In specific embodiments, the host is a mouse, rabbit, goat, guinea pig, chicken, rat, hamster, pig, sheep, dog or cat. In preferred embodiments, the host is a mammal. In most preferred embodiments, the host is a human.

Having generally described the invention, the same will be more readily understood by reference to the following examples, which are provided by way of illustration and are not intended as limiting.

Examples

Example 1: Isolation of a Selected cDNA Clone From the Deposited Sample

Each cDNA clone in a cited ATCC deposit is contained in a plasmid vector. Table 1A identifies the vectors used to construct the cDNA library from which each clone was isolated. In many cases, the vector used to construct the library is a phage vector from which a plasmid has been excised. The table immediately below

correlates the related plasmid for each phage vector used in constructing the cDNA library. For example, where a particular clone is identified in Table 1A as being isolated in the vector "Lambda Zap," the corresponding deposited clone is in "pBluescript."

| | | |
|----|--|--|
| 5 | <u>Vector Used to Construct Library</u> | <u>Corresponding Deposited Plasmid</u> |
| | Lambda Zap | pBluescript (pBS) |
| | Uni-Zap XR | pBluescript (pBS) |
| | Zap Express | pBK |
| | lafmid BA | plafmid BA |
| 10 | pSport1 | pSport1 |
| | pCMVSPORT 2.0 | pCMVSPORT 2.0 |
| | pCMVSPORT 3.0 | pCMVSPORT 3.0 |
| | pCR [®] 2.1 | pCR [®] 2.1 |
| 15 | <p>Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128, 256 and 5,286,636), Zap Express (U.S. Patent Nos. 5,128,256 and 5,286,636), pBluescript (pBS) (Short, J. M. et al., Nucleic Acids Res. 16:7583-7600 (1988); Alting-Mees, M. A. and Short, J. M., Nucleic Acids Res. 17:9494 (1989)) and pBK (Alting-Mees, M. A. et al., Strategies 5:58-61 (1992)) are</p> | |
| 20 | <p>commercially available from Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037. pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene. Both can be transformed into E. coli strain XL-1 Blue, also available from Stratagene. pBS comes in 4 forms SK+, SK-, KS+ and KS. The S and K refers to the orientation of the polylinker to the T7 and T3</p> | |
| 25 | <p>primer sequences which flank the polylinker region ("S" is for SacI and "K" is for KpnI which are the first sites on each respective end of the linker). "+" or "-" refer to the orientation of the f1 origin of replication ("ori"), such that in one orientation, single stranded rescue initiated from the f1 ori generates sense strand DNA and in the other, antisense.</p> | |
| 30 | <p>Vectors pSport1, pCMVSPORT 2.0 and pCMVSPORT 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into E. coli strain</p> | |

DH10B, also available from Life Technologies. (See, for instance, Gruber, C. E., et al., *Focus* 15:59 (1993).) Vector lacmid BA (Bento Soares, Columbia University, NY) contains an ampicillin resistance gene and can be transformed into *E. coli* strain XL-1 Blue. Vector pCR[®]2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed into *E. coli* strain DH10B, available from Life Technologies. (See, for instance, Clark, J. M., *Nuc. Acids Res.* 16:9677-9686 (1988) and Mead, D. et al., *Bio/Technology* 9: (1991).) Preferably, a polynucleotide of the present invention does not comprise the phage vector sequences identified for the particular clone in Table 1A, as well as the corresponding plasmid vector sequences designated above.

The deposited material in the sample assigned the ATCC Deposit Number cited in Table 1A for any given cDNA clone also may contain one or more additional plasmids, each comprising a cDNA clone different from that given clone. Thus, deposits sharing the same ATCC Deposit Number contain at least a plasmid for each cDNA clone identified in Table 1A. Typically, each ATCC deposit sample cited in Table 1A comprises a mixture of approximately equal amounts (by weight) of about 50 plasmid DNAs, each containing a different cDNA clone; but such a deposit sample may include plasmids for more or less than 50 cDNA clones, up to about 500 cDNA clones.

Two approaches can be used to isolate a particular clone from the deposited sample of plasmid DNAs cited for that clone in Table 1A. First, a plasmid is directly isolated by screening the clones using a polynucleotide probe corresponding to SEQ ID NO:X.

Particularly, a specific polynucleotide with 30-40 nucleotides is synthesized using an Applied Biosystems DNA synthesizer according to the sequence reported. The oligonucleotide is labeled, for instance, with ³²P-γ-ATP using T4 polynucleotide kinase and purified according to routine methods. (E.g., Maniatis et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Press, Cold Spring, NY (1982).) The plasmid mixture is transformed into a suitable host, as indicated above (such as XL-1 Blue (Stratagene)) using techniques known to those of skill in the art, such as those provided by the vector supplier or in related publications or patents cited above. The transformants are plated on 1.5% agar plates (containing the appropriate selection

agent, e.g., ampicillin) to a density of about 150 transformants (colonies) per plate. These plates are screened using Nylon membranes according to routine methods for bacterial colony screening (e.g., Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd Edit., (1989), Cold Spring Harbor Laboratory Press, pages 1.93 to 1.104), or other techniques known to those of skill in the art.

Alternatively, two primers of 17-20 nucleotides derived from both ends of the SEQ ID NO:X (i.e., within the region of SEQ ID NO:X bounded by the 5' NT and the 3' NT of the clone defined in Table 1A) are synthesized and used to amplify the desired cDNA using the deposited cDNA plasmid as a template. The polymerase chain reaction is carried out under routine conditions, for instance, in 25 ul of reaction mixture with 0.5 ug of the above cDNA template. A convenient reaction mixture is 1.5-5 mM MgCl₂, 0.01% (w/v) gelatin, 20 uM each of dATP, dCTP, dGTP, dTTP, 25 pmol of each primer and 0.25 Unit of Taq polymerase. Thirty five cycles of PCR (denaturation at 94 degree C for 1 min; annealing at 55 degree C for 1 min; elongation at 72 degree C for 1 min) are performed with a Perkin-Elmer Cetus automated thermal cycler. The amplified product is analyzed by agarose gel electrophoresis and the DNA band with expected molecular weight is excised and purified. The PCR product is verified to be the selected sequence by subcloning and sequencing the DNA product.

Several methods are available for the identification of the 5' or 3' non-coding portions of a gene which may not be present in the deposited clone. These methods include but are not limited to, filter probing, clone enrichment using specific probes, and protocols similar or identical to 5' and 3' "RACE" protocols which are well known in the art. For instance, a method similar to 5' RACE is available for generating the missing 5' end of a desired full-length transcript. (Fromont-Racine et al., *Nucleic Acids Res.* 21(7):1683-1684 (1993).)

Briefly, a specific RNA oligonucleotide is ligated to the 5' ends of a population of RNA presumably containing full-length gene RNA transcripts. A primer set containing a primer specific to the ligated RNA oligonucleotide and a primer specific to a known sequence of the gene of interest is used to PCR amplify the 5' portion of the desired full-length gene. This amplified product may then be sequenced and used to generate the full length gene.

This above method starts with total RNA isolated from the desired source, although poly-A+ RNA can be used. The RNA preparation can then be treated with phosphatase if necessary to eliminate 5' phosphate groups on degraded or damaged RNA which may interfere with the later RNA ligase step. The phosphatase should
5 then be inactivated and the RNA treated with tobacco acid pyrophosphatase in order to remove the cap structure present at the 5' ends of messenger RNAs. This reaction leaves a 5' phosphate group at the 5' end of the cap cleaved RNA which can then be ligated to an RNA oligonucleotide using T4 RNA ligase.

This modified RNA preparation is used as a template for first strand cDNA
10 synthesis using a gene specific oligonucleotide. The first strand synthesis reaction is used as a template for PCR amplification of the desired 5' end using a primer specific to the ligated RNA oligonucleotide and a primer specific to the known sequence of the gene of interest. The resultant product is then sequenced and analyzed to confirm that the 5' end sequence belongs to the desired gene.

Example 2: Isolation of Genomic Clones Corresponding to a Polynucleotide

A human genomic P1 library (Genomic Systems, Inc.) is screened by PCR
using primers selected for the cDNA sequence corresponding to SEQ ID NO:X., according to the method described in Example 1. (See also, Sambrook.)

Example 3: Tissue Distribution of Polypeptide

Tissue distribution of mRNA expression of polynucleotides of the present invention is determined using protocols for Northern blot analysis, described by, among others, Sambrook et al. For example, a cDNA probe produced by the method
25 described in Example 1 is labeled with P³² using the rediprime™ DNA labeling system (Amersham Life Science), according to manufacturer's instructions. After labeling, the probe is purified using CHROMA SPIN-100™ column (Clontech Laboratories, Inc.), according to manufacturer's protocol number PT1200-1. The purified labeled probe is then used to examine various human tissues for mRNA
30 expression.

Multiple Tissue Northern (MTN) blots containing various human tissues (H) or human immune system tissues (IM) (Clontech) are examined with the labeled

probe using ExpressHyb™ hybridization solution (Clontech) according to manufacturer's protocol number PT1190-1. Following hybridization and washing, the blots are mounted and exposed to film at -70 degree C overnight, and the films developed according to standard procedures.

5

Example 4: Chromosomal Mapping of the Polynucleotides

An oligonucleotide primer set is designed according to the sequence at the 5' end of SEQ ID NO:X. This primer preferably spans about 100 nucleotides. This primer set is then used in a polymerase chain reaction under the following set of conditions : 30 seconds, 95 degree C; 1 minute, 56 degree C; 1 minute, 70 degree C. This cycle is repeated 32 times followed by one 5 minute cycle at 70 degree C. Human, mouse, and hamster DNA is used as template in addition to a somatic cell hybrid panel containing individual chromosomes or chromosome fragments (Bios, Inc). The reactions is analyzed on either 8% polyacrylamide gels or 3.5 % agarose gels. Chromosome mapping is determined by the presence of an approximately 100 bp PCR fragment in the particular somatic cell hybrid.

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Example 5: Bacterial Expression of a Polypeptide

A polynucleotide encoding a polypeptide of the present invention is amplified using PCR oligonucleotide primers corresponding to the 5' and 3' ends of the DNA sequence, as outlined in Example 1, to synthesize insertion fragments. The primers used to amplify the cDNA insert should preferably contain restriction sites, such as BamHI and XbaI, at the 5' end of the primers in order to clone the amplified product into the expression vector. For example, BamHI and XbaI correspond to the restriction enzyme sites on the bacterial expression vector pQE-9. (Qiagen, Inc., Chatsworth, CA). This plasmid vector encodes antibiotic resistance (Amp^r), a bacterial origin of replication (ori), an IPTG-regulatable promoter/operator (P/O), a ribosome binding site (RBS), a 6-histidine tag (6-His), and restriction enzyme cloning sites.

20

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The pQE-9 vector is digested with BamHI and XbaI and the amplified fragment is ligated into the pQE-9 vector maintaining the reading frame initiated at the bacterial RBS. The ligation mixture is then used to transform the E. coli strain

M15/rep4 (Qiagen, Inc.) which contains multiple copies of the plasmid pREP4, which expresses the lacI repressor and also confers kanamycin resistance (Kan^r).

Transformants are identified by their ability to grow on LB plates and ampicillin/kanamycin resistant colonies are selected. Plasmid DNA is isolated and confirmed by restriction analysis.

Clones containing the desired constructs are grown overnight (O/N) in liquid culture in LB media supplemented with both Amp (100 ug/ml) and Kan (25 ug/ml). The O/N culture is used to inoculate a large culture at a ratio of 1:100 to 1:250. The cells are grown to an optical density 600 (O.D.⁶⁰⁰) of between 0.4 and 0.6. IPTG (Isopropyl-B-D-thiogalacto pyranoside) is then added to a final concentration of 1 mM. IPTG induces by inactivating the lacI repressor, clearing the P/O leading to increased gene expression.

Cells are grown for an extra 3 to 4 hours. Cells are then harvested by centrifugation (20 mins at 6000Xg). The cell pellet is solubilized in the chaotropic agent 6 Molar Guanidine HCl by stirring for 3-4 hours at 4 degree C. The cell debris is removed by centrifugation, and the supernatant containing the polypeptide is loaded onto a nickel-nitrilo-tri-acetic acid ("Ni-NTA") affinity resin column (available from QIAGEN, Inc., *supra*). Proteins with a 6 x His tag bind to the Ni-NTA resin with high affinity and can be purified in a simple one-step procedure (for details see: The QIAexpressionist (1995) QIAGEN, Inc., *supra*).

Briefly, the supernatant is loaded onto the column in 6 M guanidine-HCl, pH 8, the column is first washed with 10 volumes of 6 M guanidine-HCl, pH 8, then washed with 10 volumes of 6 M guanidine-HCl pH 6, and finally the polypeptide is eluted with 6 M guanidine-HCl, pH 5.

The purified protein is then renatured by dialyzing it against phosphate-buffered saline (PBS) or 50 mM Na-acetate, pH 6 buffer plus 200 mM NaCl. Alternatively, the protein can be successfully refolded while immobilized on the Ni-NTA column. The recommended conditions are as follows: renature using a linear 6M-1M urea gradient in 500 mM NaCl, 20% glycerol, 20 mM Tris/HCl pH 7.4, containing protease inhibitors. The renaturation should be performed over a period of 1.5 hours or more. After renaturation the proteins are eluted by the addition of 250 mM imidazole. Imidazole is removed by a final dialyzing step against PBS or 50

mM sodium acetate pH 6 buffer plus 200 mM NaCl. The purified protein is stored at 4 degree C or frozen at -80 degree C.

In addition to the above expression vector, the present invention further includes an expression vector comprising phage operator and promoter elements operatively linked to a polynucleotide of the present invention, called pHE4a. (ATCC
5 Accession Number 209645, deposited on February 25, 1998.) This vector contains:
1) a neomycinphosphotransferase gene as a selection marker, 2) an *E. coli* origin of replication, 3) a T5 phage promoter sequence, 4) two lac operator sequences, 5) a Shine-Delgarno sequence, and 6) the lactose operon repressor gene (*lacIq*). The
10 origin of replication (*oriC*) is derived from pUC19 (LTI, Gaithersburg, MD). The promoter sequence and operator sequences are made synthetically.

DNA can be inserted into the pHEa by restricting the vector with NdeI and XbaI, BamHI, XhoI, or Asp718, running the restricted product on a gel, and isolating the larger fragment (the stuffer fragment should be about 310 base pairs). The DNA
15 insert is generated according to the PCR protocol described in Example 1, using PCR primers having restriction sites for NdeI (5' primer) and XbaI, BamHI, XhoI, or Asp718.(3' primer). The PCR insert is gel purified and restricted with compatible enzymes. The insert and vector are ligated according to standard protocols.

The engineered vector could easily be substituted in the above protocol to
20 express protein in a bacterial system.

Example 6: Purification of a Polypeptide from an Inclusion Body

The following alternative method can be used to purify a polypeptide expressed in *E. coli* when it is present in the form of inclusion bodies. Unless
25 otherwise specified, all of the following steps are conducted at 4-10 degree C.

Upon completion of the production phase of the *E. coli* fermentation, the cell culture is cooled to 4-10 degree C and the cells harvested by continuous centrifugation at 15,000 rpm (Heraeus Sepatech). On the basis of the expected yield of protein per unit weight of cell paste and the amount of purified protein required, an
30 appropriate amount of cell paste, by weight, is suspended in a buffer solution containing 100 mM Tris, 50 mM EDTA, pH 7.4. The cells are dispersed to a homogeneous suspension using a high shear mixer.

The cells are then lysed by passing the solution through a microfluidizer (Microfluidics, Corp. or APV Gaulin, Inc.) twice at 4000-6000 psi. The homogenate is then mixed with NaCl solution to a final concentration of 0.5 M NaCl, followed by centrifugation at 7000 xg for 15 min. The resultant pellet is washed again using 0.5M NaCl, 100 mM Tris, 50 mM EDTA, pH 7.4.

The resulting washed inclusion bodies are solubilized with 1.5 M guanidine hydrochloride (GuHCl) for 2-4 hours. After 7000 xg centrifugation for 15 min., the pellet is discarded and the polypeptide containing supernatant is incubated at 4 degree C overnight to allow further GuHCl extraction.

Following high speed centrifugation (30,000 xg) to remove insoluble particles, the GuHCl solubilized protein is refolded by quickly mixing the GuHCl extract with 20 volumes of buffer containing 50 mM sodium, pH 4.5, 150 mM NaCl, 2 mM EDTA by vigorous stirring. The refolded diluted protein solution is kept at 4 degree C without mixing for 12 hours prior to further purification steps.

To clarify the refolded polypeptide solution, a previously prepared tangential filtration unit equipped with 0.16 um membrane filter with appropriate surface area (e.g., Filtron), equilibrated with 40 mM sodium acetate, pH 6.0 is employed. The filtered sample is loaded onto a cation exchange resin (e.g., Poros HS-50, Perseptive Biosystems). The column is washed with 40 mM sodium acetate, pH 6.0 and eluted with 250 mM, 500 mM, 1000 mM, and 1500 mM NaCl in the same buffer, in a stepwise manner. The absorbance at 280 nm of the effluent is continuously monitored. Fractions are collected and further analyzed by SDS-PAGE.

Fractions containing the polypeptide are then pooled and mixed with 4 volumes of water. The diluted sample is then loaded onto a previously prepared set of tandem columns of strong anion (Poros HQ-50, Perseptive Biosystems) and weak anion (Poros CM-20, Perseptive Biosystems) exchange resins. The columns are equilibrated with 40 mM sodium acetate, pH 6.0. Both columns are washed with 40 mM sodium acetate, pH 6.0, 200 mM NaCl. The CM-20 column is then eluted using a 10 column volume linear gradient ranging from 0.2 M NaCl, 50 mM sodium acetate, pH 6.0 to 1.0 M NaCl, 50 mM sodium acetate, pH 6.5. Fractions are collected under constant A_{280} monitoring of the effluent. Fractions containing the polypeptide (determined, for instance, by 16% SDS-PAGE) are then pooled.

The resultant polypeptide should exhibit greater than 95% purity after the above refolding and purification steps. No major contaminant bands should be observed from Commassie blue stained 16% SDS-PAGE gel when 5 ug of purified protein is loaded. The purified protein can also be tested for endotoxin/LPS contamination, and typically the LPS content is less than 0.1 ng/ml according to LAL assays.

Example 7: Cloning and Expression of a Polypeptide in a Baculovirus

Expression System

10 In this example, the plasmid shuttle vector pA2 is used to insert a polynucleotide into a baculovirus to express a polypeptide. This expression vector contains the strong polyhedrin promoter of the *Autographa californica* nuclear polyhedrosis virus (AcMNPV) followed by convenient restriction sites such as BamHI, Xba I and Asp718. The polyadenylation site of the simian virus 40 ("SV40") is used for efficient polyadenylation. For easy selection of recombinant virus, the 15 plasmid contains the beta-galactosidase gene from *E. coli* under control of a weak *Drosophila* promoter in the same orientation, followed by the polyadenylation signal of the polyhedrin gene. The inserted genes are flanked on both sides by viral sequences for cell-mediated homologous recombination with wild-type viral DNA to generate a viable virus that express the cloned polynucleotide. 20

Many other baculovirus vectors can be used in place of the vector above, such as pAc373, pVL941, and pAcIM1, as one skilled in the art would readily appreciate, as long as the construct provides appropriately located signals for transcription, translation, secretion and the like, including a signal peptide and an in-frame AUG as 25 required. Such vectors are described, for instance, in Luckow et al., Virology 170:31-39 (1989).

Specifically, the cDNA sequence contained in the deposited clone, including the AUG initiation codon and the naturally associated leader sequence identified in Table 1A, is amplified using the PCR protocol described in Example 1. If the 30 naturally occurring signal sequence is used to produce the secreted protein, the pA2 vector does not need a second signal peptide. Alternatively, the vector can be modified (pA2 GP) to include a baculovirus leader sequence, using the standard

methods described in Summers et al., "A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures," Texas Agricultural Experimental Station Bulletin No. 1555 (1987).

The amplified fragment is isolated from a 1% agarose gel using a
5 commercially available kit ("GeneClean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

The plasmid is digested with the corresponding restriction enzymes and optionally, can be dephosphorylated using calf intestinal phosphatase, using routine
10 procedures known in the art. The DNA is then isolated from a 1% agarose gel using a commercially available kit ("GeneClean" BIO 101 Inc., La Jolla, Ca.).

The fragment and the dephosphorylated plasmid are ligated together with T4 DNA ligase. *E. coli* HB101 or other suitable *E. coli* hosts such as XL-1 Blue (Stratagene Cloning Systems, La Jolla, CA) cells are transformed with the ligation
15 mixture and spread on culture plates. Bacteria containing the plasmid are identified by digesting DNA from individual colonies and analyzing the digestion product by gel electrophoresis. The sequence of the cloned fragment is confirmed by DNA sequencing.

Five ug of a plasmid containing the polynucleotide is co-transfected with 1.0
20 ug of a commercially available linearized baculovirus DNA ("BaculoGold™ baculovirus DNA", Pharmingen, San Diego, CA), using the lipofection method described by Felgner et al., Proc. Natl. Acad. Sci. USA 84:7413-7417 (1987). One ug of BaculoGold™ virus DNA and 5 ug of the plasmid are mixed in a sterile well of a microtiter plate containing 50 ul of serum-free Grace's medium (Life Technologies
25 Inc., Gaithersburg, MD). Afterwards, 10 ul Lipofectin plus 90 ul Grace's medium are added, mixed and incubated for 15 minutes at room temperature. Then the transfection mixture is added drop-wise to Sf9 insect cells (ATCC CRL 1711) seeded in a 35 mm tissue culture plate with 1 ml Grace's medium without serum. The plate is then incubated for 5 hours at 27 degrees C. The transfection solution is then removed
30 from the plate and 1 ml of Grace's insect medium supplemented with 10% fetal calf serum is added. Cultivation is then continued at 27 degrees C for four days.

After four days the supernatant is collected and a plaque assay is performed, as described by Summers and Smith, *supra*. An agarose gel with "Blue Gal" (Life Technologies Inc., Gaithersburg) is used to allow easy identification and isolation of gal-expressing clones, which produce blue-stained plaques. (A detailed description of a "plaque assay" of this type can also be found in the user's guide for insect cell culture and baculovirology distributed by Life Technologies Inc., Gaithersburg, page 9-10.) After appropriate incubation, blue stained plaques are picked with the tip of a micropipettor (e.g., Eppendorf). The agar containing the recombinant viruses is then resuspended in a microcentrifuge tube containing 200 ul of Grace's medium and the suspension containing the recombinant baculovirus is used to infect Sf9 cells seeded in 35 mm dishes. Four days later the supernatants of these culture dishes are harvested and then they are stored at 4 degree C.

To verify the expression of the polypeptide, Sf9 cells are grown in Grace's medium supplemented with 10% heat-inactivated FBS. The cells are infected with the recombinant baculovirus containing the polynucleotide at a multiplicity of infection ("MOI") of about 2. If radiolabeled proteins are desired, 6 hours later the medium is removed and is replaced with SF900 II medium minus methionine and cysteine (available from Life Technologies Inc., Rockville, MD). After 42 hours, 5 uCi of ^{35}S -methionine and 5 uCi ^{35}S -cysteine (available from Amersham) are added. The cells are further incubated for 16 hours and then are harvested by centrifugation. The proteins in the supernatant as well as the intracellular proteins are analyzed by SDS-PAGE followed by autoradiography (if radiolabeled).

Microsequencing of the amino acid sequence of the amino terminus of purified protein may be used to determine the amino terminal sequence of the produced protein.

Example 8: Expression of a Polypeptide in Mammalian Cells

The polypeptide of the present invention can be expressed in a mammalian cell. A typical mammalian expression vector contains a promoter element, which mediates the initiation of transcription of mRNA, a protein coding sequence, and signals required for the termination of transcription and polyadenylation of the transcript. Additional elements include enhancers, Kozak sequences and intervening

sequences flanked by donor and acceptor sites for RNA splicing. Highly efficient transcription is achieved with the early and late promoters from SV40, the long terminal repeats (LTRs) from Retroviruses, e.g., RSV, HTLV, HIV and the early promoter of the cytomegalovirus (CMV). However, cellular elements can also be
5 used (e.g., the human actin promoter).

Suitable expression vectors for use in practicing the present invention include, for example, vectors such as pSVL and pMSG (Pharmacia, Uppsala, Sweden), pRSVcat (ATCC 37152), pSV2dhfr (ATCC 37146), pBC12MI (ATCC 67109), pCMVSPORT 2.0, and pCMVSPORT 3.0. Mammalian host cells that could be used
10 include, human Hela, 293, H9 and Jurkat cells, mouse NIH3T3 and C127 cells, Cos 1, Cos 7 and CV1, quail QC1-3 cells, mouse L cells and Chinese hamster ovary (CHO) cells.

Alternatively, the polypeptide can be expressed in stable cell lines containing the polynucleotide integrated into a chromosome. The co-transfection with a
15 selectable marker such as dhfr, gpt, neomycin, hygromycin allows the identification and isolation of the transfected cells.

The transfected gene can also be amplified to express large amounts of the encoded protein. The DHFR (dihydrofolate reductase) marker is useful in developing cell lines that carry several hundred or even several thousand copies of the gene of
20 interest. (See, e.g., Alt, F. W., et al., J. Biol. Chem. 253:1357-1370 (1978); Hamlin, J. L. and Ma, C., Biochem. et Biophys. Acta, 1097:107-143 (1990); Page, M. J. and Sydenham, M. A., Biotechnology 9:64-68 (1991).) Another useful selection marker is the enzyme glutamine synthase (GS) (Murphy et al., Biochem J. 227:277-279 (1991); Bebbington et al., Bio/Technology 10:169-175 (1992). Using these markers,
25 the mammalian cells are grown in selective medium and the cells with the highest resistance are selected. These cell lines contain the amplified gene(s) integrated into a chromosome. Chinese hamster ovary (CHO) and NSO cells are often used for the production of proteins.

Derivatives of the plasmid pSV2-dhfr (ATCC Accession No. 37146), the
30 expression vectors pC4 (ATCC Accession No. 209646) and pC6 (ATCC Accession No. 209647) contain the strong promoter (LTR) of the Rous Sarcoma Virus (Cullen et al., Molecular and Cellular Biology, 438-447 (March, 1985)) plus a fragment of the

CMV-enhancer (Boshart et al., Cell 41:521-530 (1985).) Multiple cloning sites, e.g., with the restriction enzyme cleavage sites BamHI, XbaI and Asp718, facilitate the cloning of the gene of interest. The vectors also contain the 3' intron, the polyadenylation and termination signal of the rat preproinsulin gene, and the mouse DHFR gene under control of the SV40 early promoter.

Specifically, the plasmid pC6, for example, is digested with appropriate restriction enzymes and then dephosphorylated using calf intestinal phosphates by procedures known in the art. The vector is then isolated from a 1% agarose gel.

A polynucleotide of the present invention is amplified according to the protocol outlined in Example 1. If the naturally occurring signal sequence is used to produce the secreted protein, the vector does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)

The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("GeneClean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

The amplified fragment is then digested with the same restriction enzyme and purified on a 1% agarose gel. The isolated fragment and the dephosphorylated vector are then ligated with T4 DNA ligase. *E. coli* HB101 or XL-1 Blue cells are then transformed and bacteria are identified that contain the fragment inserted into plasmid pC6 using, for instance, restriction enzyme analysis.

Chinese hamster ovary cells lacking an active DHFR gene is used for transfection. Five μ g of the expression plasmid pC6 a pC4 is cotransfected with 0.5 μ g of the plasmid pSVneo using lipofectin (Felgner et al., *supra*). The plasmid pSV2-neo contains a dominant selectable marker, the *neo* gene from Tn5 encoding an enzyme that confers resistance to a group of antibiotics including G418. The cells are seeded in alpha minus MEM supplemented with 1 mg/ml G418. After 2 days, the cells are trypsinized and seeded in hybridoma cloning plates (Greiner, Germany) in alpha minus MEM supplemented with 10, 25, or 50 ng/ml of methotrexate plus 1 mg/ml G418. After about 10-14 days single clones are trypsinized and then seeded in 6-well petri dishes or 10 ml flasks using different concentrations of methotrexate (50

nM, 100 nM, 200 nM, 400 nM, 800 nM). Clones growing at the highest concentrations of methotrexate are then transferred to new 6-well plates containing even higher concentrations of methotrexate (1 uM, 2 uM, 5 uM, 10 mM, 20 mM). The same procedure is repeated until clones are obtained which grow at a concentration of 100 - 200 uM. Expression of the desired gene product is analyzed, for instance, by SDS-PAGE and Western blot or by reversed phase HPLC analysis.

Example 9: Protein Fusions

The polypeptides of the present invention are preferably fused to other proteins. These fusion proteins can be used for a variety of applications. For example, fusion of the present polypeptides to His-tag, HA-tag, protein A, IgG domains, and maltose binding protein facilitates purification. (See Example 5; see also EP A 394,827; Traunecker, et al., Nature 331:84-86 (1988).) Similarly, fusion to IgG-1, IgG-3, and albumin increases the half-life time in vivo. Nuclear localization signals fused to the polypeptides of the present invention can target the protein to a specific subcellular localization, while covalent heterodimer or homodimers can increase or decrease the activity of a fusion protein. Fusion proteins can also create chimeric molecules having more than one function. Finally, fusion proteins can increase solubility and/or stability of the fused protein compared to the non-fused protein. All of the types of fusion proteins described above can be made by modifying the following protocol, which outlines the fusion of a polypeptide to an IgG molecule, or the protocol described in Example 5.

Briefly, the human Fc portion of the IgG molecule can be PCR amplified, using primers that span the 5' and 3' ends of the sequence described below. These primers also should have convenient restriction enzyme sites that will facilitate cloning into an expression vector, preferably a mammalian expression vector.

For example, if pC4 (Accession No. 209646) is used, the human Fc portion can be ligated into the BamHI cloning site. Note that the 3' BamHI site should be destroyed. Next, the vector containing the human Fc portion is re-restricted with BamHI, linearizing the vector, and a polynucleotide of the present invention, isolated by the PCR protocol described in Example 1, is ligated into this BamHI site. Note

that the polynucleotide is cloned without a stop codon, otherwise a fusion protein will not be produced.

If the naturally occurring signal sequence is used to produce the secreted protein, pC4 does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)

Human IgG Fc region:

```
GGGATCCGGAGCCCAAATCTTCTGACAAAACCTCACACATGCCCACC
10 GTGCCCAGCACCTGAATTCGAGGGTGCACCGTCAGTCTTCCTCTTCCCCC
AAAACCCAAGGACACCCTCATGATCTCCCGGACTCCTGAGGTCACATGCG
TGGTGGTGGACGTAAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTAC
GTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGC
AGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAG
15 GACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCT
CCCAACCCCCATCGAGAAAACCATCTCCAAGCCAAAGGGCAGCCCCGA
GAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAA
CCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCAAGCGACATCG
CCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCAC
20 GCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCAC
CGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGA
TGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCT
CCGGGTAAATGAGTGCGACGGCCGCGACTCTAGAGGAT (SEQ ID NO:1)
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25 **Example 10: Production of an Antibody from a Polypeptide**

The antibodies of the present invention can be prepared by a variety of methods. (See, Current Protocols, Chapter 2.) As one example of such methods, cells expressing a polypeptide of the present invention is administered to an animal to induce the production of sera containing polyclonal antibodies. In a preferred method, a preparation of the secreted protein is prepared and purified to render it substantially free of natural contaminants. Such a preparation is then introduced into an animal in order to produce polyclonal antisera of greater specific activity.

In the most preferred method, the antibodies of the present invention are monoclonal antibodies (or protein binding fragments thereof). Such monoclonal antibodies can be prepared using hybridoma technology. (Köhler et al., Nature 256:495 (1975); Köhler et al., Eur. J. Immunol. 6:511 (1976); Köhler et al., Eur. J. Immunol. 6:292 (1976); Hammerling et al., in: Monoclonal Antibodies and T-Cell Hybridomas, Elsevier, N.Y., pp. 563-681 (1981).) In general, such procedures involve immunizing an animal (preferably a mouse) with polypeptide or, more preferably, with a secreted polypeptide-expressing cell. Such cells may be cultured in any suitable tissue culture medium; however, it is preferable to culture cells in Earle's modified Eagle's medium supplemented with 10% fetal bovine serum (inactivated at about 56 degrees C), and supplemented with about 10 g/l of nonessential amino acids, about 1,000 U/ml of penicillin, and about 100 ug/ml of streptomycin.

The splenocytes of such mice are extracted and fused with a suitable myeloma cell line. Any suitable myeloma cell line may be employed in accordance with the present invention; however, it is preferable to employ the parent myeloma cell line (SP2O), available from the ATCC. After fusion, the resulting hybridoma cells are selectively maintained in HAT medium, and then cloned by limiting dilution as described by Wands et al. (Gastroenterology 80:225-232 (1981).) The hybridoma cells obtained through such a selection are then assayed to identify clones which secrete antibodies capable of binding the polypeptide.

Alternatively, additional antibodies capable of binding to the polypeptide can be produced in a two-step procedure using anti-idiotypic antibodies. Such a method makes use of the fact that antibodies are themselves antigens, and therefore, it is possible to obtain an antibody which binds to a second antibody. In accordance with this method, protein specific antibodies are used to immunize an animal, preferably a mouse. The splenocytes of such an animal are then used to produce hybridoma cells, and the hybridoma cells are screened to identify clones which produce an antibody whose ability to bind to the protein-specific antibody can be blocked by the polypeptide. Such antibodies comprise anti-idiotypic antibodies to the protein-specific antibody and can be used to immunize an animal to induce formation of further protein-specific antibodies.

It will be appreciated that Fab and F(ab')₂ and other fragments of the antibodies of the present invention may be used according to the methods disclosed herein. Such fragments are typically produced by proteolytic cleavage, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')₂ fragments). Alternatively, secreted protein-binding fragments can be produced through the application of recombinant DNA technology or through synthetic chemistry.

For in vivo use of antibodies in humans, it may be preferable to use "humanized" chimeric monoclonal antibodies. Such antibodies can be produced using genetic constructs derived from hybridoma cells producing the monoclonal antibodies described above. Methods for producing chimeric antibodies are known in the art. (See, for review, Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., WO 8702671; Boulianne et al., Nature 312:643 (1984); Neuberger et al., Nature 314:268 (1985).)

Example 11: Production Of Secreted Protein For High-Throughput Screening Assays

The following protocol produces a supernatant containing a polypeptide to be tested. This supernatant can then be used in the Screening Assays described herein.

First, dilute Poly-D-Lysine (644 587 Boehringer-Mannheim) stock solution (1mg/ml in PBS) 1:20 in PBS (w/o calcium or magnesium 17-516F Biowhittaker) for a working solution of 50ug/ml. Add 200 ul of this solution to each well (24 well plates) and incubate at RT for 20 minutes. Be sure to distribute the solution over each well (note: a 12-channel pipetter may be used with tips on every other channel). Aspirate off the Poly-D-Lysine solution and rinse with 1ml PBS (Phosphate Buffered Saline). The PBS should remain in the well until just prior to plating the cells and plates may be poly-lysine coated in advance for up to two weeks.

Plate 293T cells (do not carry cells past P+20) at 2×10^5 cells/well in .5ml DMEM(Dulbecco's Modified Eagle Medium)(with 4.5 G/L glucose and L-glutamine

(12-604F Biowhittaker))/10% heat inactivated FBS(14-503F Biowhittaker)/1x Penstrep(17-602E Biowhittaker). Let the cells grow overnight.

The next day, mix together in a sterile solution basin: 300 ul Lipofectamine (18324-012 Gibco/BRL) and 5ml Optimem I (31985070 Gibco/BRL)/96-well plate.

- 5 With a small volume multi-channel pipetter, aliquot approximately 2ug of an expression vector containing a polynucleotide insert, produced by the methods described in Examples 8 or 9, into an appropriately labeled 96-well round bottom plate. With a multi-channel pipetter, add 50ul of the Lipofectamine/Optimem I mixture to each well. Pipette up and down gently to mix. Incubate at RT 15-45
- 10 minutes. After about 20 minutes, use a multi-channel pipetter to add 150ul Optimem I to each well. As a control, one plate of vector DNA lacking an insert should be transfected with each set of transfections.

- Preferably, the transfection should be performed by tag-teaming the following tasks. By tag-teaming, hands on time is cut in half, and the cells do not spend too
- 15 much time on PBS. First, person A aspirates off the media from four 24-well plates of cells, and then person B rinses each well with .5-1ml PBS. Person A then aspirates off PBS rinse, and person B, using a 12-channel pipetter with tips on every other channel, adds the 200ul of DNA/Lipofectamine/Optimem I complex to the odd wells first, then to the even wells, to each row on the 24-well plates. Incubate at 37 degrees
- 20 C for 6 hours.

- While cells are incubating, prepare appropriate media, either 1%BSA in DMEM with 1x penstrep, or CHO-5 media (116.6 mg/L of CaCl₂ (anhyd); 0.00130 mg/L CuSO₄·5H₂O; 0.050 mg/L of Fe(NO₃)₃·9H₂O; 0.417 mg/L of FeSO₄·7H₂O; 311.80 mg/L of KCl; 28.64 mg/L of MgCl₂; 48.84 mg/L of MgSO₄; 6995.50 mg/L of
- 25 NaCl; 2400.0 mg/L of NaHCO₃; 62.50 mg/L of NaH₂PO₄·H₂O; 71.02 mg/L of Na₂HPO₄; .4320 mg/L of ZnSO₄·7H₂O; .002 mg/L of Arachidonic Acid ; 1.022 mg/L of Cholesterol; .070 mg/L of DL-alpha-Tocopherol-Acetate; 0.0520 mg/L of Linoleic Acid; 0.010 mg/L of Linolenic Acid; 0.010 mg/L of Myristic Acid; 0.010 mg/L of Oleic Acid; 0.010 mg/L of Palmitric Acid; 0.010 mg/L of Palmitic Acid; 100 mg/L of
- 30 Pluronic F-68; 0.010 mg/L of Stearic Acid; 2.20 mg/L of Tween 80; 4551 mg/L of D-Glucose; 130.85 mg/ml of L- Alanine; 147.50 mg/ml of L-Arginine-HCL; 7.50 mg/ml of L-Asparagine-H₂O; 6.65 mg/ml of L-Aspartic Acid; 29.56 mg/ml of L-Cystine-

2HCL-H₂O; 31.29 mg/ml of L-Cystine-2HCL; 7.35 mg/ml of L-Glutamic Acid; 365.0 mg/ml of L-Glutamine; 18.75 mg/ml of Glycine; 52.48 mg/ml of L-Histidine-HCL-H₂O; 106.97 mg/ml of L-Isoleucine; 111.45 mg/ml of L-Leucine; 163.75 mg/ml of L-Lysine HCL; 32.34 mg/ml of L-Methionine; 68.48 mg/ml of L-Phenylalanine; 40.0
5 mg/ml of L-Proline; 26.25 mg/ml of L-Serine; 101.05 mg/ml of L-Threonine; 19.22 mg/ml of L-Tryptophan; 91.79 mg/ml of L-Tyrosine-2Na-2H₂O; 99.65 mg/ml of L-Valine; 0.0035 mg/L of Biotin; 3.24 mg/L of D-Ca Pantothenate; 11.78 mg/L of Choline Chloride; 4.65 mg/L of Folic Acid; 15.60 mg/L of i-Inositol; 3.02 mg/L of Niacinamide; 3.00 mg/L of Pyridoxal HCL; 0.031 mg/L of Pyridoxine HCL; 0.319
10 mg/L of Riboflavin; 3.17 mg/L of Thiamine HCL; 0.365 mg/L of Thymidine; and 0.680 mg/L of Vitamin B₁₂; 25 mM of HEPES Buffer; 2.39 mg/L of Na Hypoxanthine; 0.105 mg/L of Lipoic Acid; 0.081 mg/L of Sodium Putrescine-2HCL; 55.0 mg/L of Sodium Pyruvate; 0.0067 mg/L of Sodium Selenite; 20uM of Ethanolamine; 0.122 mg/L of Ferric Citrate; 41.70 mg/L of Methyl-B-Cyclodextrin
15 complexed with Linoleic Acid; 33.33 mg/L of Methyl-B-Cyclodextrin complexed with Oleic Acid; and 10 mg/L of Methyl-B-Cyclodextrin complexed with Retinal) with 2mm glutamine and 1x penstrep. (BSA (81-068-3 Bayer) 100gm dissolved in 1L DMEM for a 10% BSA stock solution). Filter the media and collect 50 ul for endotoxin assay in 15ml polystyrene conical.

20 The transfection reaction is terminated, preferably by tag-teaming, at the end of the incubation period. Person A aspirates off the transfection media, while person B adds 1.5ml appropriate media to each well. Incubate at 37 degrees C for 45 or 72 hours depending on the media used: 1%BSA for 45 hours or CHO-5 for 72 hours.

On day four, using a 300ul multichannel pipetter, aliquot 600ul in one 1ml
25 deep well plate and the remaining supernatant into a 2ml deep well. The supernatants from each well can then be used in the assays described in Examples 13-20.

It is specifically understood that when activity is obtained in any of the assays described below using a supernatant, the activity originates from either the polypeptide directly (e.g., as a secreted protein) or by the polypeptide inducing
30 expression of other proteins, which are then secreted into the supernatant. Thus, the invention further provides a method of identifying the protein in the supernatant characterized by an activity in a particular assay.

Example 12: Construction of GAS Reporter Construct

One signal transduction pathway involved in the differentiation and proliferation of cells is called the Jaks-STATs pathway. Activated proteins in the Jaks-STATs pathway bind to gamma activation site "GAS" elements or interferon-sensitive responsive element ("ISRE"), located in the promoter of many genes. The binding of a protein to these elements alter the expression of the associated gene.

GAS and ISRE elements are recognized by a class of transcription factors called Signal Transducers and Activators of Transcription, or "STATs." There are six members of the STATs family. Stat1 and Stat3 are present in many cell types, as is Stat2 (as response to IFN-alpha is widespread). Stat4 is more restricted and is not in many cell types though it has been found in T helper class I, cells after treatment with IL-12. Stat5 was originally called mammary growth factor, but has been found at higher concentrations in other cells including myeloid cells. It can be activated in tissue culture cells by many cytokines.

The STATs are activated to translocate from the cytoplasm to the nucleus upon tyrosine phosphorylation by a set of kinases known as the Janus Kinase ("Jaks") family. Jaks represent a distinct family of soluble tyrosine kinases and include Tyk2, Jak1, Jak2, and Jak3. These kinases display significant sequence similarity and are generally catalytically inactive in resting cells.

The Jaks are activated by a wide range of receptors summarized in the Table below. (Adapted from review by Schidler and Darnell, Ann. Rev. Biochem. 64:621-51 (1995).) A cytokine receptor family, capable of activating Jaks, is divided into two groups: (a) Class 1 includes receptors for IL-2, IL-3, IL-4, IL-6, IL-7, IL-9, IL-11, IL-12, IL-15, Epo, PRL, GH, G-CSF, GM-CSF, LIF, CNTF, and thrombopoietin; and (b) Class 2 includes IFN-a, IFN-g, and IL-10. The Class 1 receptors share a conserved cysteine motif (a set of four conserved cysteines and one tryptophan) and a WSXWS motif (a membrane proximal region encoding Trp-Ser-Xxx-Trp-Ser (SEQ ID NO:2)).

Thus, on binding of a ligand to a receptor, Jaks are activated, which in turn activate STATs, which then translocate and bind to GAS elements. This entire process is encompassed in the Jaks-STATs signal transduction pathway.

- Therefore, activation of the Jaks-STATs pathway, reflected by the binding of the GAS or the ISRE element, can be used to indicate proteins involved in the proliferation and differentiation of cells. For example, growth factors and cytokines are known to activate the Jaks-STATs pathway. (See Table below.) Thus, by using
- 5 GAS elements linked to reporter molecules, activators of the Jaks-STATs pathway can be identified.

| | | <u>JAKs</u> | | | | | <u>STATS</u> | <u>GAS(elements) or ISRE</u> |
|----|--|----------------------------------|-------------|-------------|-------------|-------------|--------------|------------------------------|
| | | <u>Ligand</u> | <u>tyk2</u> | <u>Jak1</u> | <u>Jak2</u> | <u>Jak3</u> | | |
| | | <u>IFN family</u> | | | | | | |
| 5 | | IFN- α /B | + | - | - | 1,2,3 | | ISRE |
| | | IFN-g | | + | + | - | 1 | GAS (IRF1>Lys6>IFP) |
| | | IL-10 | + | ? | ? | - | 1,3 | |
| | | <u>gp130 family</u> | | | | | | |
| 10 | | IL-6 (Pleiotrophic) | + | + | + | ? | 1,3 | GAS (IRF1>Lys6>IFP) |
| | | IL-11(Pleiotrophic) | ? | + | ? | ? | 1,3 | |
| | | OnM(Pleiotrophic) | ? | + | + | ? | 1,3 | |
| | | LIF(Pleiotrophic) ? | + | + | ? | 1,3 | | |
| | | CNTF(Pleiotrophic) | -/+ | + | + | ? | 1,3 | |
| 15 | | G-CSF(Pleiotrophic) | ? | + | ? | ? | 1,3 | |
| | | IL-12(Pleiotrophic) | + | - | + | + | 1,3 | |
| | | <u>g-C family</u> | | | | | | |
| 20 | | IL-2 (lymphocytes) | - | + | - | + | 1,3,5 | GAS |
| | | IL-4 (lymph/myeloid) | - | + | - | + | 6 | GAS (IRF1 = IFP >>Ly6)(IgH) |
| | | IL-7 (lymphocytes) | - | + | - | + | 5 | GAS |
| | | IL-9 (lymphocytes) | - | + | - | + | 5 | GAS |
| | | IL-13 (lymphocyte) | - | + | ? | ? | 6 | GAS |
| | | IL-15 | ? | + | ? | + | 5 | GAS |
| 25 | | <u>gp140 family</u> | | | | | | |
| | | IL-3 (myeloid) | - | - | + | - | 5 | GAS (IRF1>IFP>>Ly6) |
| | | IL-5 (myeloid) | - | - | + | - | 5 | GAS |
| | | GM-CSF (myeloid) | - | - | + | - | 5 | GAS |
| 30 | | <u>Growth hormone family</u> | | | | | | |
| | | GH | ? | - | + | - | 5 | |
| | | PRL | ? | +/- | + | - | 1,3,5 | |
| | | EPO | ? | - | + | - | 5 | GAS(B-CAS>IRF1=IFP>>Ly6) |
| 35 | | <u>Receptor Tyrosine Kinases</u> | | | | | | |
| | | EGF | ? | + | + | - | 1,3 | GAS (IRF1) |
| | | PDGF | ? | + | + | - | 1,3 | |
| | | CSF-1 | ? | + | + | - | 1,3 | GAS (not IRF1) |

To construct a synthetic GAS containing promoter element, which is used in the Biological Assays described in Examples 13-14, a PCR based strategy is employed to generate a GAS-SV40 promoter sequence. The 5' primer contains four tandem copies of the GAS binding site found in the IRF1 promoter and previously demonstrated to bind STATs upon induction with a range of cytokines (Rothman et al., Immunity 1:457-468 (1994).), although other GAS or ISRE elements can be used instead. The 5' primer also contains 18bp of sequence complementary to the SV40 early promoter sequence and is flanked with an XhoI site. The sequence of the 5' primer is:

10 5':GCGCCTCGAGATTTCCTCCGAAATCTAGATTTCCTCCGAAATGATTTCCTCCGAAATGATTTCCTCCGAAATATCTGCCATCTCAATTAG:3' (SEQ ID NO:3)

The downstream primer is complementary to the SV40 promoter and is flanked with a Hind III site: 5':GCGGCAAGCTTTTTTGCAAAGCCTAGGC:3'

15 (SEQ ID NO:4)

PCR amplification is performed using the SV40 promoter template present in the B-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI/Hind III and subcloned into BLSK2-. (Stratagene.) Sequencing with forward and reverse primers confirms that the insert contains the following sequence:

20 5':CTCGAGATTTCCTCCGAAATCTAGATTTCCTCCGAAATGATTTCCTCCGAAATGATTTCCTCCGAAATATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCGCCCCTAACTCCGCCCATCCCGCCCCTAACTCCGCCCAGTTCCGCCCCA
TTCTCCGCCCCATGGCTGACTAATTTTTTTTATTTATGCAGAGGCCGAGGC
25 CGCCTCGGCCTCTGAGCTATTCCAGAAGTAGTGAGGAGGCTTTTTTTGGAGGCCTAGGCTTTTGCAAAAAAGCTT:3' (SEQ ID NO:5)

With this GAS promoter element linked to the SV40 promoter, a GAS:SEAP2 reporter construct is next engineered. Here, the reporter molecule is a secreted alkaline phosphatase, or "SEAP." Clearly, however, any reporter molecule can be instead of SEAP, in this or in any of the other Examples. Well known reporter molecules that can be used instead of SEAP include chloramphenicol

acetyltransferase (CAT), luciferase, alkaline phosphatase, B-galactosidase, green fluorescent protein (GFP), or any protein detectable by an antibody.

The above sequence confirmed synthetic GAS-SV40 promoter element is subcloned into the pSEAP-Promoter vector obtained from Clontech using HindIII and XhoI, effectively replacing the SV40 promoter with the amplified GAS:SV40 promoter element, to create the GAS-SEAP vector. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

Thus, in order to generate mammalian stable cell lines expressing the GAS-SEAP reporter, the GAS-SEAP cassette is removed from the GAS-SEAP vector using SalI and NotI, and inserted into a backbone vector containing the neomycin resistance gene, such as pGFP-1 (Clontech), using these restriction sites in the multiple cloning site, to create the GAS-SEAP/Neo vector. Once this vector is transfected into mammalian cells, this vector can then be used as a reporter molecule for GAS binding as described in Examples 13-14.

Other constructs can be made using the above description and replacing GAS with a different promoter sequence. For example, construction of reporter molecules containing NFK-B and EGR promoter sequences are described in Examples 15 and 16. However, many other promoters can be substituted using the protocols described in these Examples. For instance, SRE, IL-2, NFAT, or Osteocalcin promoters can be substituted, alone or in combination (e.g., GAS/NF-KB/EGR, GAS/NF-KB, IL-2/NFAT, or NF-KB/GAS). Similarly, other cell lines can be used to test reporter construct activity, such as HELA (epithelial), HUVEC (endothelial), Reh (B-cell), Saos-2 (osteoblast), HUVAC (aortic), or Cardiomyocyte.

Example 13: High-Throughput Screening Assay for T-cell Activity.

The following protocol is used to assess T-cell activity by identifying factors, and determining whether supernate containing a polypeptide of the invention proliferates and/or differentiates T-cells. T-cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 12. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The T-cell used in this assay is Jurkat T-cells (ATCC Accession No. TIB-152),

although Molt-3 cells (ATCC Accession No. CRL-1552) and Molt-4 cells (ATCC Accession No. CRL-1582) cells can also be used.

Jurkat T-cells are lymphoblastic CD4+ Th1 helper cells. In order to generate stable cell lines, approximately 2 million Jurkat cells are transfected with the GAS-SEAP/neo vector using DMRIE-C (Life Technologies)(transfection procedure described below). The transfected cells are seeded to a density of approximately 20,000 cells per well and transfectants resistant to 1 mg/ml gentamicin selected. Resistant colonies are expanded and then tested for their response to increasing concentrations of interferon gamma. The dose response of a selected clone is demonstrated.

Specifically, the following protocol will yield sufficient cells for 75 wells containing 200 ul of cells. Thus, it is either scaled up, or performed in multiple to generate sufficient cells for multiple 96 well plates. Jurkat cells are maintained in RPMI + 10% serum with 1% Pen-Strep. Combine 2.5 mls of OPTI-MEM (Life Technologies) with 10 ug of plasmid DNA in a T25 flask. Add 2.5 ml OPTI-MEM containing 50 ul of DMRIE-C and incubate at room temperature for 15-45 mins.

During the incubation period, count cell concentration, spin down the required number of cells (10^7 per transfection), and resuspend in OPTI-MEM to a final concentration of 10^7 cells/ml. Then add 1ml of 1×10^7 cells in OPTI-MEM to T25 flask and incubate at 37 degrees C for 6 hrs. After the incubation, add 10 ml of RPMI + 15% serum.

The Jurkat:GAS-SEAP stable reporter lines are maintained in RPMI + 10% serum, 1 mg/ml Gentamicin, and 1% Pen-Strep. These cells are treated with supernatants containing polypeptides of the invention and/or induced polypeptides of the invention as produced by the protocol described in Example 11.

On the day of treatment with the supernatant, the cells should be washed and resuspended in fresh RPMI + 10% serum to a density of 500,000 cells per ml. The exact number of cells required will depend on the number of supernatants being screened. For one 96 well plate, approximately 10 million cells (for 10 plates, 100 million cells) are required.

Transfer the cells to a triangular reservoir boat, in order to dispense the cells into a 96 well dish, using a 12 channel pipette. Using a 12 channel pipette, transfer 200 ul of cells into each well (therefore adding 100,000 cells per well).

After all the plates have been seeded, 50 ul of the supernatants are transferred
5 directly from the 96 well plate containing the supernatants into each well using a 12 channel pipette. In addition, a dose of exogenous interferon gamma (0.1, 1.0, 10 ng) is added to wells H9, H10, and H11 to serve as additional positive controls for the assay.

The 96 well dishes containing Jurkat cells treated with supernatants are placed
10 in an incubator for 48 hrs (note: this time is variable between 48-72 hrs). 35 ul samples from each well are then transferred to an opaque 96 well plate using a 12 channel pipette. The opaque plates should be covered (using sellophene covers) and stored at -20 degrees C until SEAP assays are performed according to Example 17. The plates containing the remaining treated cells are placed at 4 degrees C and serve
15 as a source of material for repeating the assay on a specific well if desired.

As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate Jurkat T cells. Over 30 fold induction is typically observed in the positive control wells.

The above protocol may be used in the generation of both transient, as well as,
20 stable transfected cells, which would be apparent to those of skill in the art.

Example 14: High-Throughput Screening Assay Identifying Myeloid Activity

The following protocol is used to assess myeloid activity by determining whether polypeptides of the invention proliferates and/or differentiates myeloid cells.
25 Myeloid cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 12. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The myeloid cell used in this assay is U937, a pre-monocyte cell line, although TF-1, HL60, or KG1 can be used.

To transiently transfect U937 cells with the GAS/SEAP/Neo construct
30 produced in Example 12, a DEAE-Dextran method (Kharbanda et. al., 1994, Cell Growth & Differentiation, 5:259-265) is used. First, harvest 2×10^7 U937 cells and wash with PBS. The U937 cells are usually grown in RPMI 1640 medium containing

10% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 mg/ml streptomycin.

Next, suspend the cells in 1 ml of 20 mM Tris-HCl (pH 7.4) buffer containing 0.5 mg/ml DEAE-Dextran, 8 ug GAS-SEAP2 plasmid DNA, 140 mM NaCl, 5 mM
5 KCl, 375 uM Na₂HPO₄·7H₂O, 1 mM MgCl₂, and 675 uM CaCl₂. Incubate at 37 degrees C for 45 min.

Wash the cells with RPMI 1640 medium containing 10% FBS and then resuspend in 10 ml complete medium and incubate at 37 degrees C for 36 hr.

The GAS-SEAP/U937 stable cells are obtained by growing the cells in 400
10 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 400 ug/ml G418 for couple of passages.

These cells are tested by harvesting 1×10^8 cells (this is enough for ten 96-well plates assay) and wash with PBS. Suspend the cells in 200 ml above described growth medium, with a final density of 5×10^5 cells/ml. Plate 200 ul cells per well in
15 the 96-well plate (or 1×10^5 cells/well).

Add 50 ul of the supernatant prepared by the protocol described in Example 11. Incubate at 37 degrees C for 48 to 72 hr. As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate U937 cells. Over 30 fold induction is typically observed in the positive control wells. SEAP assay the
20 supernatant according to the protocol described in Example 17.

Example 15: High-Throughput Screening Assay Identifying Neuronal Activity.

When cells undergo differentiation and proliferation, a group of genes are activated through many different signal transduction pathways. One of these genes,
25 EGR1 (early growth response gene 1), is induced in various tissues and cell types upon activation. The promoter of EGR1 is responsible for such induction. Using the EGR1 promoter linked to reporter molecules, activation of cells can be assessed.

Particularly, the following protocol is used to assess neuronal activity in PC12 cell lines. PC12 cells (rat phenochromocytoma cells) are known to proliferate and/or
30 differentiate by activation with a number of mitogens, such as TPA (tetradecanoyl phorbol acetate), NGF (nerve growth factor), and EGF (epidermal growth factor). The EGR1 gene expression is activated during this treatment. Thus, by stably

transfecting PC12 cells with a construct containing an EGR promoter linked to SEAP reporter, activation of PC12 cells can be assessed.

The EGR/SEAP reporter construct can be assembled by the following protocol. The EGR-1 promoter sequence (-633 to +1)(Sakamoto K et al., Oncogene
5 6:867-871 (1991)) can be PCR amplified from human genomic DNA using the following primers:

5' GCGCTCGAGGGATGACAGCGATAGAACCCCGG -3' (SEQ ID NO:6)

5' GCGAAGCTTCGCGACTCCCCGGATCCGCCTC-3' (SEQ ID NO:7)

Using the GAS:SEAP/Neo vector produced in Example 12, EGR1 amplified
10 product can then be inserted into this vector. Linearize the GAS:SEAP/Neo vector using restriction enzymes XhoI/HindIII, removing the GAS/SV40 stuffer. Restrict the EGR1 amplified product with these same enzymes. Ligate the vector and the EGR1 promoter.

To prepare 96 well-plates for cell culture, two mls of a coating solution (1:30
15 dilution of collagen type I (Upstate Biotech Inc. Cat#08-115) in 30% ethanol (filter sterilized)) is added per one 10 cm plate or 50 ml per well of the 96-well plate, and allowed to air dry for 2 hr.

PC12 cells are routinely grown in RPMI-1640 medium (Bio Whittaker) containing 10% horse serum (JRH BIOSCIENCES, Cat. # 12449-78P), 5% heat-
20 inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 ug/ml streptomycin on a precoated 10 cm tissue culture dish. One to four split is done every three to four days. Cells are removed from the plates by scraping and resuspended with pipetting up and down for more than 15 times.

Transfect the EGR/SEAP/Neo construct into PC12 using the Lipofectamine
25 protocol described in Example 11. EGR-SEAP/PC12 stable cells are obtained by growing the cells in 300 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 300 ug/ml G418 for couple of passages.

To assay for neuronal activity, a 10 cm plate with cells around 70 to 80%
30 confluent is screened by removing the old medium. Wash the cells once with PBS (Phosphate buffered saline). Then starve the cells in low serum medium (RPMI-1640 containing 1% horse serum and 0.5% FBS with antibiotics) overnight.

The next morning, remove the medium and wash the cells with PBS. Scrape off the cells from the plate, suspend the cells well in 2 ml low serum medium. Count the cell number and add more low serum medium to reach final cell density as 5×10^5 cells/ml.

- 5 Add 200 μ l of the cell suspension to each well of 96-well plate (equivalent to 1×10^5 cells/well). Add 50 μ l supernatant produced by Example 11, 37°C for 48 to 72 hr. As a positive control, a growth factor known to activate PC12 cells through EGR can be used, such as 50 ng/ μ l of Neuronal Growth Factor (NGF). Over fifty-fold induction of SEAP is typically seen in the positive control wells. SEAP assay the
10 supernatant according to Example 17.

Example 16: High-Throughput Screening Assay for T-cell Activity

- NF-KB (Nuclear Factor KB) is a transcription factor activated by a wide variety of agents including the inflammatory cytokines IL-1 and TNF, CD30 and
15 CD40, lymphotoxin-alpha and lymphotoxin-beta, by exposure to LPS or thrombin, and by expression of certain viral gene products. As a transcription factor, NF-KB regulates the expression of genes involved in immune cell activation, control of apoptosis (NF- KB appears to shield cells from apoptosis), B and T-cell development, anti-viral and antimicrobial responses, and multiple stress responses.

- 20 In non-stimulated conditions, NF- KB is retained in the cytoplasm with I-KB (Inhibitor KB). However, upon stimulation, I- KB is phosphorylated and degraded, causing NF- KB to shuttle to the nucleus, thereby activating transcription of target genes. Target genes activated by NF- KB include IL-2, IL-6, GM-CSF, ICAM-1 and class 1 MHC.

- 25 Due to its central role and ability to respond to a range of stimuli, reporter constructs utilizing the NF-KB promoter element are used to screen the supernatants produced in Example 11. Activators or inhibitors of NF-KB would be useful in treating diseases. For example, inhibitors of NF-KB could be used to treat those diseases related to the acute or chronic activation of NF-KB, such as rheumatoid
30 arthritis.

To construct a vector containing the NF-KB promoter element, a PCR based strategy is employed. The upstream primer contains four tandem copies of the NF-

KB binding site (GGGGACTTTCCC) (SEQ ID NO:8), 18 bp of sequence complementary to the 5' end of the SV40 early promoter sequence, and is flanked with an XhoI site:

5' : GCGGCCTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCC
5 GGGACTTTCCATCCTGCCATCTCAATTAG:3' (SEQ ID NO:9)

The downstream primer is complementary to the 3' end of the SV40 promoter and is flanked with a Hind III site:

5' : GCGGCAAGCTTTTTTGCAAAGCCTAGGC:3' (SEQ ID NO:4)

10 PCR amplification is performed using the SV40 promoter template present in the pB-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI and Hind III and subcloned into BLSK2-. (Stratagene) Sequencing with the T7 and T3 primers confirms the insert contains the following sequence:

15 5' : CTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGAC
TTTCCATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCGCCCCTAACTC
CGCCCATCCCGCCCCTAACTCCGCCAGTTCGGCCCATTTCTCCGCCCCATG
GCTGACTAATTTTTTTTATTTATGCAGAGGCCGAGGCCGCTCGGCCTCTG
AGCTATTCCAGAAGTAGTGAGGAGGCTTTTTTGGAGGCCTAGGCTTTTGC
20 AAAAAGCTT:3' (SEQ ID NO:10)

Next, replace the SV40 minimal promoter element present in the pSEAP2-promoter plasmid (Clontech) with this NF-KB/SV40 fragment using XhoI and HindIII. However, this vector does not contain a neomycin resistance gene, and
25 therefore, is not preferred for mammalian expression systems.

In order to generate stable mammalian cell lines, the NF-KB/SV40/SEAP cassette is removed from the above NF-KB/SEAP vector using restriction enzymes SalI and NotI, and inserted into a vector containing neomycin resistance. Particularly, the NF-KB/SV40/SEAP cassette was inserted into pGFP-1 (Clontech), replacing the
30 GFP gene, after restricting pGFP-1 with SalI and NotI.

Once NF-KB/SV40/SEAP/Neo vector is created, stable Jurkat T-cells are created and maintained according to the protocol described in Example 13. Similarly,

the method for assaying supernatants with these stable Jurkat T-cells is also described in Example 13. As a positive control, exogenous TNF alpha (0.1, 1, 10 ng) is added to wells H9, H10, and H11, with a 5-10 fold activation typically observed.

5 **Example 17: Assay for SEAP Activity**

As a reporter molecule for the assays described in Examples 13-16, SEAP activity is assayed using the Tropix Phospho-light Kit (Cat. BP-400) according to the following general procedure. The Tropix Phospho-light Kit supplies the Dilution, Assay, and Reaction Buffers used below.

- 10 Prime a dispenser with the 2.5x Dilution Buffer and dispense 15 ul of 2.5x dilution buffer into Optiplates containing 35 ul of a supernatant. Seal the plates with a plastic sealer and incubate at 65 degree C for 30 min. Separate the Optiplates to avoid uneven heating.

- Cool the samples to room temperature for 15 minutes. Empty the dispenser
15 and prime with the Assay Buffer. Add 50 ml Assay Buffer and incubate at room temperature 5 min. Empty the dispenser and prime with the Reaction Buffer (see the table below): Add 50 ul Reaction Buffer and incubate at room temperature for 20 minutes. Since the intensity of the chemiluminescent signal is time dependent, and it takes about 10 minutes to read 5 plates on luminometer, one should treat 5 plates at
20 each time and start the second set 10 minutes later.

Read the relative light unit in the luminometer. Set H12 as blank, and print the results. An increase in chemiluminescence indicates reporter activity.

Reaction Buffer Formulation:

| # of plates | Rxn buffer diluent (ml) | CSPD (ml) |
|-------------|-------------------------|-----------|
| 10 | 60 | 3 |
| 11 | 65 | 3.25 |
| 12 | 70 | 3.5 |
| 13 | 75 | 3.75 |
| 14 | 80 | 4 |
| 15 | 85 | 4.25 |
| 16 | 90 | 4.5 |
| 17 | 95 | 4.75 |
| 18 | 100 | 5 |
| 19 | 105 | 5.25 |
| 20 | 110 | 5.5 |

| | | |
|----|-----|-------|
| 21 | 115 | 5.75 |
| 22 | 120 | 6 |
| 23 | 125 | 6.25 |
| 24 | 130 | 6.5 |
| 25 | 135 | 6.75 |
| 26 | 140 | 7 |
| 27 | 145 | 7.25 |
| 28 | 150 | 7.5 |
| 29 | 155 | 7.75 |
| 30 | 160 | 8 |
| 31 | 165 | 8.25 |
| 32 | 170 | 8.5 |
| 33 | 175 | 8.75 |
| 34 | 180 | 9 |
| 35 | 185 | 9.25 |
| 36 | 190 | 9.5 |
| 37 | 195 | 9.75 |
| 38 | 200 | 10 |
| 39 | 205 | 10.25 |
| 40 | 210 | 10.5 |
| 41 | 215 | 10.75 |
| 42 | 220 | 11 |
| 43 | 225 | 11.25 |
| 44 | 230 | 11.5 |
| 45 | 235 | 11.75 |
| 46 | 240 | 12 |
| 47 | 245 | 12.25 |
| 48 | 250 | 12.5 |
| 49 | 255 | 12.75 |
| 50 | 260 | 13 |

Example 18: High-Throughput Screening Assay Identifying Changes in Small Molecule Concentration and Membrane Permeability

Binding of a ligand to a receptor is known to alter intracellular levels of small molecules, such as calcium, potassium, sodium, and pH, as well as alter membrane potential. These alterations can be measured in an assay to identify supernatants which bind to receptors of a particular cell. Although the following protocol describes an assay for calcium, this protocol can easily be modified to detect changes in potassium, sodium, pH, membrane potential, or any other small molecule which is detectable by a fluorescent probe.

The following assay uses Fluorometric Imaging Plate Reader ("FLIPR") to measure changes in fluorescent molecules (Molecular Probes) that bind small

molecules. Clearly, any fluorescent molecule detecting a small molecule can be used instead of the calcium fluorescent molecule, fluo-4 (Molecular Probes, Inc.; catalog no. F-14202), used here.

For adherent cells, seed the cells at 10,000 -20,000 cells/well in a Co-star
5 black 96-well plate with clear bottom. The plate is incubated in a CO₂ incubator for 20 hours. The adherent cells are washed two times in Biotek washer with 200 ul of HBSS (Hank's Balanced Salt Solution) leaving 100 ul of buffer after the final wash.

A stock solution of 1 mg/ml fluo-4 is made in 10% pluronic acid DMSO. To
load the cells with fluo-4, 50 ul of 12 ug/ml fluo-4 is added to each well. The plate
10 is incubated at 37 degrees C in a CO₂ incubator for 60 min. The plate is washed four times in the Biotek washer with HBSS leaving 100 ul of buffer.

For non-adherent cells, the cells are spun down from culture media. Cells are
re-suspended to $2-5 \times 10^6$ cells/ml with HBSS in a 50-ml conical tube. 4 ul of 1 mg/ml
fluo-4 solution in 10% pluronic acid DMSO is added to each ml of cell suspension.
15 The tube is then placed in a 37 degrees C water bath for 30-60 min. The cells are washed twice with HBSS, resuspended to 1×10^6 cells/ml, and dispensed into a microplate, 100 ul/well. The plate is centrifuged at 1000 rpm for 5 min. The plate is then washed once in Denley CellWash with 200 ul, followed by an aspiration step to 100 ul final volume.

20 For a non-cell based assay, each well contains a fluorescent molecule, such as fluo-4. The supernatant is added to the well, and a change in fluorescence is detected.

To measure the fluorescence of intracellular calcium, the FLIPR is set for the
following parameters: (1) System gain is 300-800 mW; (2) Exposure time is 0.4
25 second; (3) Camera F/stop is F/2; (4) Excitation is 488 nm; (5) Emission is 530 nm;
and (6) Sample addition is 50 ul. Increased emission at 530 nm indicates an
extracellular signaling event which has resulted in an increase in the intracellular
Ca⁺⁺ concentration.

30 **Example 19: High-Throughput Screening Assay Identifying Tyrosine Kinase Activity**

The Protein Tyrosine Kinases (PTK) represent a diverse group of transmembrane and cytoplasmic kinases. Within the Receptor Protein Tyrosine Kinase (RPTK) group are receptors for a range of mitogenic and metabolic growth factors including the PDGF, FGF, EGF, NGF, HGF and Insulin receptor subfamilies.

- 5 In addition there are a large family of RPTKs for which the corresponding ligand is unknown. Ligands for RPTKs include mainly secreted small proteins, but also membrane-bound and extracellular matrix proteins.

Activation of RPTK by ligands involves ligand-mediated receptor dimerization, resulting in transphosphorylation of the receptor subunits and activation
10 of the cytoplasmic tyrosine kinases. The cytoplasmic tyrosine kinases include receptor associated tyrosine kinases of the src-family (e.g., src, yes, lck, lyn, fyn) and non-receptor linked and cytosolic protein tyrosine kinases, such as the Jak family, members of which mediate signal transduction triggered by the cytokine superfamily of receptors (e.g., the Interleukins, Interferons, GM-CSF, and Leptin).

- 15 Because of the wide range of known factors capable of stimulating tyrosine kinase activity, the identification of novel human secreted proteins capable of activating tyrosine kinase signal transduction pathways are of interest. Therefore, the following protocol is designed to identify those novel human secreted proteins capable of activating the tyrosine kinase signal transduction pathways.

- 20 Seed target cells (e.g., primary keratinocytes) at a density of approximately 25,000 cells per well in a 96 well Loprodyne Silent Screen Plates purchased from Nalge Nunc (Naperville, IL). The plates are sterilized with two 30 minute rinses with 100% ethanol, rinsed with water and dried overnight. Some plates are coated for 2 hr with 100 ml of cell culture grade type I collagen (50 mg/ml), gelatin (2%) or
25 polylysine (50 mg/ml), all of which can be purchased from Sigma Chemicals (St. Louis, MO) or 10% Matrigel purchased from Becton Dickinson (Bedford, MA), or calf serum, rinsed with PBS and stored at 4 degree C. Cell growth on these plates is assayed by seeding 5,000 cells/well in growth medium and indirect quantitation of cell number through use of alamarBlue as described by the manufacturer Alamar
30 Biosciences, Inc. (Sacramento, CA) after 48 hr. Falcon plate covers #3071 from Becton Dickinson (Bedford, MA) are used to cover the Loprodyne Silent Screen

Plates. Falcon Microtest III cell culture plates can also be used in some proliferation experiments.

To prepare extracts, A431 cells are seeded onto the nylon membranes of Loprodyn plates (20,000/200ml/well) and cultured overnight in complete medium.

- 5 Cells are quiesced by incubation in serum-free basal medium for 24 hr. After 5-20 minutes treatment with EGF (60ng/ml) or 50 ul of the supernatant produced in Example 11, the medium was removed and 100 ml of extraction buffer ((20 mM HEPES pH 7.5, 0.15 M NaCl, 1% Triton X-100, 0.1% SDS, 2 mM Na₃VO₄, 2 mM Na₄P₂O₇ and a cocktail of protease inhibitors (# 1836170) obtained from
- 10 Boehringer Mannheim (Indianapolis, IN) is added to each well and the plate is shaken on a rotating shaker for 5 minutes at 4 degrees C. The plate is then placed in a vacuum transfer manifold and the extract filtered through the 0.45 mm membrane bottoms of each well using house vacuum. Extracts are collected in a 96-well catch/assay plate in the bottom of the vacuum manifold and immediately placed on
- 15 ice. To obtain extracts clarified by centrifugation, the content of each well, after detergent solubilization for 5 minutes, is removed and centrifuged for 15 minutes at 4 degrees C at 16,000 x g.

Test the filtered extracts for levels of tyrosine kinase activity. Although many methods of detecting tyrosine kinase activity are known, one method is described

20 here.

- Generally, the tyrosine kinase activity of a supernatant is evaluated by determining its ability to phosphorylate a tyrosine residue on a specific substrate (a biotinylated peptide). Biotinylated peptides that can be used for this purpose include PSK1 (corresponding to amino acids 6-20 of the cell division kinase cdc2-p34) and
- 25 PSK2 (corresponding to amino acids 1-17 of gastrin). Both peptides are substrates for a range of tyrosine kinases and are available from Boehringer Mannheim.

- The tyrosine kinase reaction is set up by adding the following components in order. First, add 10ul of 5uM Biotinylated Peptide, then 10ul ATP/Mg₂⁺ (5mM ATP/50mM MgCl₂), then 10ul of 5x Assay Buffer (40mM imidazole hydrochloride,
- 30 pH7.3, 40 mM beta-glycerophosphate, 1mM EGTA, 100mM MgCl₂, 5 mM MnCl₂, 0.5 mg/ml BSA), then 5ul of Sodium Vanadate(1mM), and then 5ul of water. Mix the

components gently and preincubate the reaction mix at 30 degrees C for 2 min. Initial the reaction by adding 10ul of the control enzyme or the filtered supernatant.

The tyrosine kinase assay reaction is then terminated by adding 10 ul of 120mm EDTA and place the reactions on ice.

- 5 Tyrosine kinase activity is determined by transferring 50 ul aliquot of reaction mixture to a microtiter plate (MTP) module and incubating at 37 degrees C for 20 min. This allows the streptavidin coated 96 well plate to associate with the biotinylated peptide. Wash the MTP module with 300ul/well of PBS four times. Next add 75 ul of anti-phosphotyrosine antibody conjugated to horse radish
- 10 peroxidase(anti-P-Tyr-POD(0.5u/ml)) to each well and incubate at 37 degrees C for one hour. Wash the well as above.

- Next add 100ul of peroxidase substrate solution (Boehringer Mannheim) and incubate at room temperature for at least 5 mins (up to 30 min). Measure the absorbance of the sample at 405 nm by using ELISA reader. The level of bound
- 15 peroxidase activity is quantitated using an ELISA reader and reflects the level of tyrosine kinase activity.

Example 20: High-Throughput Screening Assay Identifying Phosphorylation Activity

- 20 As a potential alternative and/or compliment to the assay of protein tyrosine kinase activity described in Example 19, an assay which detects activation (phosphorylation) of major intracellular signal transduction intermediates can also be used. For example, as described below one particular assay can detect tyrosine phosphorylation of the Erk-1 and Erk-2 kinases. However, phosphorylation of other
- 25 molecules, such as Raf, JNK, p38 MAP, Map kinase kinase (MEK), MEK kinase, Src, Muscle specific kinase (MuSK), IRAK, Tec, and Janus, as well as any other phosphoserine, phosphotyrosine, or phosphothreonine molecule, can be detected by substituting these molecules for Erk-1 or Erk-2 in the following assay.

- Specifically, assay plates are made by coating the wells of a 96-well ELISA
- 30 plate with 0.1ml of protein G (1ug/ml) for 2 hr at room temp, (RT). The plates are then rinsed with PBS and blocked with 3% BSA/PBS for 1 hr at RT. The protein G plates are then treated with 2 commercial monoclonal antibodies (100ng/well) against

Erk-1 and Erk-2 (1 hr at RT) (Santa Cruz Biotechnology). (To detect other molecules, this step can easily be modified by substituting a monoclonal antibody detecting any of the above described molecules.) After 3-5 rinses with PBS, the plates are stored at 4 degrees C until use.

5 A431 cells are seeded at 20,000/well in a 96-well Loprodyne filterplate and cultured overnight in growth medium. The cells are then starved for 48 hr in basal medium (DMEM) and then treated with EGF (6ng/well) or 50 ul of the supernatants obtained in Example 11 for 5-20 minutes. The cells are then solubilized and extracts filtered directly into the assay plate.

10 After incubation with the extract for 1 hr at RT, the wells are again rinsed. As a positive control, a commercial preparation of MAP kinase (10ng/well) is used in place of A431 extract. Plates are then treated with a commercial polyclonal (rabbit) antibody (1ug/ml) which specifically recognizes the phosphorylated epitope of the Erk-1 and Erk-2 kinases (1 hr at RT). This antibody is biotinylated by standard
15 procedures. The bound polyclonal antibody is then quantitated by successive incubations with Europium-streptavidin and Europium fluorescence enhancing reagent in the Wallac DELFIA instrument (time-resolved fluorescence). An increased fluorescent signal over background indicates a phosphorylation.

20 **Example 21: Method of Determining Alterations in a Gene Corresponding to a Polynucleotide**

 RNA isolated from entire families or individual patients presenting with a phenotype of interest (such as a disease) is be isolated. cDNA is then generated from these RNA samples using protocols known in the art. (See, Sambrook.) The cDNA
25 is then used as a template for PCR, employing primers surrounding regions of interest in SEQ ID NO:X. Suggested PCR conditions consist of 35 cycles at 95 degrees C for 30 seconds; 60-120 seconds at 52-58 degrees C; and 60-120 seconds at 70 degrees C, using buffer solutions described in Sidransky et al., Science 252:706 (1991).

 PCR products are then sequenced using primers labeled at their 5' end with T4
30 polynucleotide kinase, employing SequiTherm Polymerase. (Epicentre Technologies). The intron-exon borders of selected exons is also determined and genomic PCR products analyzed to confirm the results. PCR products harboring

suspected mutations is then cloned and sequenced to validate the results of the direct sequencing.

PCR products is cloned into T-tailed vectors as described in Holton et al., Nucleic Acids Research, 19:1156 (1991) and sequenced with T7 polymerase (United States Biochemical). Affected individuals are identified by mutations not present in unaffected individuals.

Genomic rearrangements are also observed as a method of determining alterations in a gene corresponding to a polynucleotide. Genomic clones isolated according to Example 2 are nick-translated with digoxigenindeoxy-uridine 5'-triphosphate (Boehringer Mannheim), and FISH performed as described in Johnson et al., Methods Cell Biol. 35:73-99 (1991). Hybridization with the labeled probe is carried out using a vast excess of human cot-1 DNA for specific hybridization to the corresponding genomic locus.

Chromosomes are counterstained with 4,6-diamino-2-phenylidole and propidium iodide, producing a combination of C- and R-bands. Aligned images for precise mapping are obtained using a triple-band filter set (Chroma Technology, Brattleboro, VT) in combination with a cooled charge-coupled device camera (Photometrics, Tucson, AZ) and variable excitation wavelength filters. (Johnson et al., Genet. Anal. Tech. Appl., 8:75 (1991).) Image collection, analysis and chromosomal fractional length measurements are performed using the ISee Graphical Program System. (Inovision Corporation, Durham, NC.) Chromosome alterations of the genomic region hybridized by the probe are identified as insertions, deletions, and translocations. These alterations are used as a diagnostic marker for an associated disease.

Example 22: Method of Detecting Abnormal Levels of a Polypeptide in a Biological Sample

A polypeptide of the present invention can be detected in a biological sample, and if an increased or decreased level of the polypeptide is detected, this polypeptide is a marker for a particular phenotype. Methods of detection are numerous, and thus, it is understood that one skilled in the art can modify the following assay to fit their particular needs.

For example, antibody-sandwich ELISAs are used to detect polypeptides in a sample, preferably a biological sample. Wells of a microtiter plate are coated with specific antibodies, at a final concentration of 0.2 to 10 ug/ml. The antibodies are either monoclonal or polyclonal and are produced by the method described in

- 5 Example 10. The wells are blocked so that non-specific binding of the polypeptide to the well is reduced.

The coated wells are then incubated for > 2 hours at RT with a sample containing the polypeptide. Preferably, serial dilutions of the sample should be used to validate results. The plates are then washed three times with deionized or distilled
10 water to remove unbounded polypeptide.

Next, 50 ul of specific antibody-alkaline phosphatase conjugate, at a concentration of 25-400 ng, is added and incubated for 2 hours at room temperature. The plates are again washed three times with deionized or distilled water to remove unbounded conjugate.

- 15 Add 75 ul of 4-methylumbelliferyl phosphate (MUP) or p-nitrophenyl phosphate (NPP) substrate solution to each well and incubate 1 hour at room temperature. Measure the reaction by a microtiter plate reader. Prepare a standard curve, using serial dilutions of a control sample, and plot polypeptide concentration on the X-axis (log scale) and fluorescence or absorbance of the Y-axis (linear scale).
20 Interpolate the concentration of the polypeptide in the sample using the standard curve.

Example 23: Formulation

- The invention also provides methods of treatment and/or prevention of
25 diseases or disorders (such as, for example, any one or more of the diseases or disorders disclosed herein) by administration to a subject of an effective amount of a Therapeutic. By therapeutic is meant polynucleotides or polypeptides of the invention (including fragments and variants), agonists or antagonists thereof, and/or antibodies thereto, in combination with a pharmaceutically acceptable carrier type
30 (e.g., a sterile carrier).

The Therapeutic will be formulated and dosed in a fashion consistent with good medical practice, taking into account the clinical condition of the individual

patient (especially the side effects of treatment with the Therapeutic alone), the site of delivery, the method of administration, the scheduling of administration, and other factors known to practitioners. The "effective amount" for purposes herein is thus determined by such considerations.

5 As a general proposition, the total pharmaceutically effective amount of the Therapeutic administered parenterally per dose will be in the range of about 1 µg/kg/day to 10 mg/kg/day of patient body weight, although, as noted above, this will be subject to therapeutic discretion. More preferably, this dose is at least 0.01 mg/kg/day, and most preferably for humans between about 0.01 and 1 mg/kg/day for
10 the hormone. If given continuously, the Therapeutic is typically administered at a dose rate of about 1 µg/kg/hour to about 50 µg/kg/hour, either by 1-4 injections per day or by continuous subcutaneous infusions, for example, using a mini-pump. An intravenous bag solution may also be employed. The length of treatment needed to observe changes and the interval following treatment for responses to occur appears
15 to vary depending on the desired effect.

 Therapeutics can be administered orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), buccally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid
20 filler, diluent, encapsulating material or formulation auxiliary of any. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

 Therapeutics of the invention are also suitably administered by sustained-
25 release systems. Suitable examples of sustained-release Therapeutics are administered orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), buccally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or
30 formulation auxiliary of any type. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

Therapeutics of the invention are also suitably administered by sustained-release systems. Suitable examples of sustained-release Therapeutics include suitable polymeric materials (such as, for example, semi-permeable polymer matrices in the form of shaped articles, e.g., films, or microcapsules), suitable hydrophobic materials
5 (for example as an emulsion in an acceptable oil) or ion exchange resins, and sparingly soluble derivatives (such as, for example, a sparingly soluble salt).

Sustained-release matrices include polylactides (U.S. Pat. No. 3,773,919, EP 58,481), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate (Sidman et al., Biopolymers 22:547-556 (1983)), poly (2- hydroxyethyl methacrylate) (Langer et al.,
10 J. Biomed. Mater. Res. 15:167-277 (1981), and Langer, Chem. Tech. 12:98-105 (1982)), ethylene vinyl acetate (Langer et al., Id.) or poly-D- (-)-3-hydroxybutyric acid (EP 133,988).

Sustained-release Therapeutics also include liposomally entrapped Therapeutics of the invention (*see* generally, Langer, *Science* 249:1527-1533 (1990);
15 Treat et al., in *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 317 -327 and 353-365 (1989)). Liposomes containing the Therapeutic are prepared by methods known per se: DE 3,218,121; Epstein et al., Proc. Natl. Acad. Sci. (USA) 82:3688-3692 (1985); Hwang et al., Proc. Natl. Acad. Sci.(USA) 77:4030-4034 (1980); EP 52,322; EP 36,676; EP
20 88,046; EP 143,949; EP 142,641; Japanese Pat. Appl. 83-118008; U.S. Pat. Nos. 4,485,045 and 4,544,545; and EP 102,324. Ordinarily, the liposomes are of the small (about 200-800 Angstroms) unilamellar type in which the lipid content is greater than about 30 mol. percent cholesterol, the selected proportion being adjusted for the optimal Therapeutic.

25 In yet an additional embodiment, the Therapeutics of the invention are delivered by way of a pump (*see* Langer, *supra*; Sefton, CRC Crit. Ref. Biomed. Eng. 14:201 (1987); Buchwald et al., Surgery 88:507 (1980); Saudek et al., N. Engl. J. Med. 321:574 (1989)).

Other controlled release systems are discussed in the review by Langer
30 (*Science* 249:1527-1533 (1990)).

For parenteral administration, in one embodiment, the Therapeutic is formulated generally by mixing it at the desired degree of purity, in a unit dosage

injectable form (solution, suspension, or emulsion), with a pharmaceutically acceptable carrier, i.e., one that is non-toxic to recipients at the dosages and concentrations employed and is compatible with other ingredients of the formulation. For example, the formulation preferably does not include oxidizing agents and other compounds that are known to be deleterious to the Therapeutic.

Generally, the formulations are prepared by contacting the Therapeutic uniformly and intimately with liquid carriers or finely divided solid carriers or both. Then, if necessary, the product is shaped into the desired formulation. Preferably the carrier is a parenteral carrier, more preferably a solution that is isotonic with the blood of the recipient. Examples of such carrier vehicles include water, saline, Ringer's solution, and dextrose solution. Non-aqueous vehicles such as fixed oils and ethyl oleate are also useful herein, as well as liposomes.

The carrier suitably contains minor amounts of additives such as substances that enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, succinate, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e.g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids, such as glycine, glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, manose, or dextrans; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; counterions such as sodium; and/or nonionic surfactants such as polysorbates, poloxamers, or PEG.

The Therapeutic is typically formulated in such vehicles at a concentration of about 0.1 mg/ml to 100 mg/ml, preferably 1-10 mg/ml, at a pH of about 3 to 8. It will be understood that the use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of polypeptide salts.

Any pharmaceutical used for therapeutic administration can be sterile. Sterility is readily accomplished by filtration through sterile filtration membranes (e.g., 0.2 micron membranes). Therapeutics generally are placed into a container

having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

Therapeutics ordinarily will be stored in unit or multi-dose containers, for example, sealed ampoules or vials, as an aqueous solution or as a lyophilized
5 formulation for reconstitution. As an example of a lyophilized formulation, 10-ml vials are filled with 5 ml of sterile-filtered 1% (w/v) aqueous Therapeutic solution, and the resulting mixture is lyophilized. The infusion solution is prepared by reconstituting the lyophilized Therapeutic using bacteriostatic Water-for-Injection.

The invention also provides a pharmaceutical pack or kit comprising one or
10 more containers filled with one or more of the ingredients of the Therapeutics of the invention. Associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration. In addition, the Therapeutics may be employed in
15 conjunction with other therapeutic compounds.

The Therapeutics of the invention may be administered alone or in combination with adjuvants. Adjuvants that may be administered with the Therapeutics of the invention include, but are not limited to, alum, alum plus deoxycholate (ImmunoAg), MTP-PE (Biocine Corp.), QS21 (Genentech, Inc.), BCG
20 (e.g., THERACYS®), MPL and nonviable preparations of *Corynebacterium parvum*. In a specific embodiment, Therapeutics of the invention are administered in combination with alum. In another specific embodiment, Therapeutics of the invention are administered in combination with QS-21. Further adjuvants that may be administered with the Therapeutics of the invention include, but are not limited to,
25 Monophosphoryl lipid immunomodulator, AdjuVax 100a, QS-21, QS-18, CRL1005, Aluminum salts, MF-59, and Virosomal adjuvant technology. Vaccines that may be administered with the Therapeutics of the invention include, but are not limited to, vaccines directed toward protection against MMR (measles, mumps, rubella), polio, varicella, tetanus/diphtheria, hepatitis A, hepatitis B, haemophilus influenzae B,
30 whooping cough, pneumonia, influenza, Lyme's Disease, rotavirus, cholera, yellow fever, Japanese encephalitis, poliomyelitis, rabies, typhoid fever, and pertussis. Combinations may be administered either concomitantly, e.g., as an admixture,

separately but simultaneously or concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second.

The Therapeutics of the invention may be administered alone or in combination with other therapeutic agents. Therapeutic agents that may be administered in combination with the Therapeutics of the invention, include but not limited to, chemotherapeutic agents, antibiotics, steroidal and non-steroidal anti-inflammatories, conventional immunotherapeutic agents, and/or therapeutic treatments described below. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second.

In certain embodiments, Therapeutics of the invention are administered in combination with antiretroviral agents, nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and/or protease inhibitors (PIs). NRTIs that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, RETROVIR™ (zidovudine/AZT), VIDEX™ (didanosine/ddI), HIVID™ (zalcitabine/ddC), ZERIT™ (stavudine/d4T), EPIVIR™ (lamivudine/3TC), and COMBIVIR™ (zidovudine/lamivudine). NNRTIs that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, VIRAMUNE™ (nevirapine), RESCRIPTOR™ (delavirdine), and SUSTIVA™ (efavirenz). Protease inhibitors that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, CRIXIVAN™ (indinavir), NORVIR™

(ritonavir), INVIRASE™ (saquinavir), and VIRACEPT™ (nelfinavir). In a specific embodiment, antiretroviral agents, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and/or protease inhibitors may be used in any combination with Therapeutics of the invention to treat AIDS and/or to prevent or treat HIV infection.

Additional NRTIs include LODENOSINE™ (F-ddA; an acid-stable adenosine NRTI; Triangle/Abbott); COVIRACIL™ (emtricitabine/FTC; structurally related to lamivudine (3TC) but with 3- to 10-fold greater activity *in vitro*; Triangle/Abbott); dOTC (BCH-10652, also structurally related to lamivudine but retains activity against a substantial proportion of lamivudine-resistant isolates; Biochem Pharma); Adefovir (refused approval for anti-HIV therapy by FDA; Gilead Sciences); PREVEON® (Adefovir Dipivoxil, the active prodrug of adefovir; its active form is PMEA-pp); TENOFOVIR™ (bis-POC PMPA, a PMPA prodrug; Gilead); DAPD/DXG (active metabolite of DAPD; Triangle/Abbott); D-D4FC (related to 3TC, with activity against AZT/3TC-resistant virus); GW420867X (Glaxo Wellcome); ZIAGEN™ (abacavir/159U89; Glaxo Wellcome Inc.); CS-87 (3'-azido-2',3'-dideoxyuridine; WO 99/66936); and S-acyl-2-thioethyl (SATE)-bearing prodrug forms of β -L-FD4C and β -L-FddC (WO 98/17281).

Additional NNRTIs include COACTINON™ (Emivirine/MKC-442, potent NNRTI of the HEPT class; Triangle/Abbott); CAPRAVIRINE™ (AG-1549/S-1153, a next generation NNRTI with activity against viruses containing the K103N mutation; Agouron); PNU-142721 (has 20- to 50-fold greater activity than its predecessor delavirdine and is active against K103N mutants; Pharmacia & Upjohn); DPC-961 and DPC-963 (second-generation derivatives of efavirenz, designed to be active against viruses with the K103N mutation; DuPont); GW-420867X (has 25-fold greater activity than HBV097 and is active against K103N mutants; Glaxo Wellcome); CALANOLIDE A (naturally occurring agent from the latex tree; active against viruses containing either or both the Y181C and K103N mutations); and Propolis (WO 99/49830).

Additional protease inhibitors include LOPINAVIR™ (ABT378/r; Abbott Laboratories); BMS-232632 (an azapeptide; Bristol-Myers Squibb); TIPRANAVIR™

(PNU-140690, a non-peptic dihydropyrone; Pharmacia & Upjohn); PD-178390 (a nonpeptidic dihydropyrone; Parke-Davis); BMS 232632 (an azapeptide; Bristol-Myers Squibb); L-756,423 (an indinavir analog; Merck); DMP-450 (a cyclic urea compound; Avid & DuPont); AG-1776 (a peptidomimetic with *in vitro* activity
5 against protease inhibitor-resistant viruses; Agouron); VX-175/GW-433908 (phosphate prodrug of amprenavir; Vertex & Glaxo Wellcome); CGP61755 (Ciba); and AGENERASE™ (amprenavir; Glaxo Wellcome Inc.).

Additional antiretroviral agents include fusion inhibitors/gp41 binders. Fusion inhibitors/gp41 binders include T-20 (a peptide from residues 643-678 of the
10 HIV gp41 transmembrane protein ectodomain which binds to gp41 in its resting state and prevents transformation to the fusogenic state; Trimeris) and T-1249 (a second-generation fusion inhibitor; Trimeris).

Additional antiretroviral agents include fusion inhibitors/chemokine receptor antagonists. Fusion inhibitors/chemokine receptor antagonists include CXCR4
15 antagonists such as AMD 3100 (a bicyclam), SDF-1 and its analogs, and ALX40-4C (a cationic peptide), T22 (an 18 amino acid peptide; Trimeris) and the T22 analogs T134 and T140; CCR5 antagonists such as RANTES (9-68), AOP-RANTES, NNY-RANTES, and TAK-779; and CCR5/CXCR4 antagonists such as NSC 651016 (a distamycin analog). Also included are CCR2B, CCR3, and CCR6 antagonists.
20 Chemokine receptor agonists such as RANTES, SDF-1, MIP-1 α , MIP-1 β , etc., may also inhibit fusion.

Additional antiretroviral agents include integrase inhibitors. Integrase inhibitors include dicaffeoylquinic (DFQA) acids; L-chicoric acid (a dicaffeoyltartaric (DCTA) acid); quinalizarin (QLC) and related anthraquinones;
25 ZINTEVIR™ (AR 177, an oligonucleotide that probably acts at cell surface rather than being a true integrase inhibitor; Arondex); and naphthols such as those disclosed in WO 98/50347.

Additional antiretroviral agents include hydroxyurea-like compounds such as BCX-34 (a purine nucleoside phosphorylase inhibitor; Biocryst); ribonucleotide
30 reductase inhibitors such as DIDOX™ (Molecules for Health); inosine monophosphate dehydrogenase (IMPDH) inhibitors such as VX-497 (Vertex); and mycopholic acids such as CellCept (mycophenolate mofetil; Roche).

Additional antiretroviral agents include inhibitors of viral integrase, inhibitors of viral genome nuclear translocation such as arylene bis(methylketone) compounds; inhibitors of HIV entry such as AOP-RANTES, NNY-RANTES, RANTES-IgG fusion protein, soluble complexes of RANTES and glycosaminoglycans (GAG), and
 5 AMD-3100; nucleocapsid zinc finger inhibitors such as dithiane compounds; targets of HIV Tat and Rev; and pharmacoenhancers such as ABT-378.

Other antiretroviral therapies and adjunct therapies include cytokines and lymphokines such as MIP-1 α , MIP-1 β , SDF-1 α , IL-2, PROLEUKINTM (aldesleukin/L2-7001; Chiron), IL-4, IL-10, IL-12, and IL-13; interferons such as
 10 IFN- α 2a; antagonists of TNFs, NF κ B, GM-CSF, M-CSF, and IL-10; agents that modulate immune activation such as cyclosporin and prednisone; vaccines such as RemuneTM (HIV Immunogen), APL 400-003 (Apollon), recombinant gp120 and fragments, bivalent (B/E) recombinant envelope glycoprotein, rgp120CM235, MN
 15 rgp120, SF-2 rgp120, gp120/soluble CD4 complex, Delta JR-FL protein, branched synthetic peptide derived from discontinuous gp120 C3/C4 domain, fusion-competent immunogens, and Gag, Pol, Nef, and Tat vaccines; gene-based therapies such as genetic suppressor elements (GSEs; WO 98/54366), and intrakines (genetically modified CC chemokines targetted to the ER to block surface expression of newly synthesized CCR5 (Yang *et al.*, *PNAS* 94:11567-72 (1997); Chen *et al.*,
 20 *Nat. Med.* 3:1110-16 (1997)); antibodies such as the anti-CXCR4 antibody 12G5, the anti-CCR5 antibodies 2D7, 5C7, PA8, PA9, PA10, PA11, PA12, and PA14, the anti-CD4 antibodies Q4120 and RPA-T4, the anti-CCR3 antibody 7B11, the anti-gp120 antibodies 17b, 48d, 447-52D, 257-D, 268-D and 50.1, anti-Tat antibodies, anti-TNF- α antibodies, and monoclonal antibody 33A; aryl hydrocarbon (AH) receptor
 25 agonists and antagonists such as TCDD, 3,3',4,4',5-pentachlorobiphenyl, 3,3',4,4'-tetrachlorobiphenyl, and α -naphthoflavone (WO 98/30213); and antioxidants such as γ -L-glutamyl-L-cysteine ethyl ester (γ -GCE; WO 99/56764).

In a further embodiment, the Therapeutics of the invention are administered in combination with an antiviral agent. Antiviral agents that may be administered
 30 with the Therapeutics of the invention include, but are not limited to, acyclovir, ribavirin, amantadine, and remantidine.

In other embodiments, Therapeutics of the invention may be administered in combination with anti-opportunistic infection agents. Anti-opportunistic agents that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, TRIMETHOPRIM-SULFAMETHOXAZOLE™,

5 DAPSONE™, PENTAMIDINE™, ATOVAQUONE™, ISONIAZID™, RIFAMPIN™, PYRAZINAMIDE™, ETHAMBUTOL™, RIFABUTIN™, CLARITHROMYCIN™, AZITHROMYCIN™, GANCICLOVIR™, FOSCARNET™, CIDOFOVIR™, FLUCONAZOLE™, ITRACONAZOLE™, KETOCONAZOLE™, ACYCLOVIR™, FAMCICOLVIR™, PYRIMETHAMINE™,

10 LEUCOVORIN™, NEUPOGEN™ (filgrastim/G-CSF), and LEUKINE™ (sargramostim/GM-CSF). In a specific embodiment, Therapeutics of the invention are used in any combination with TRIMETHOPRIM-SULFAMETHOXAZOLE™, DAPSONE™, PENTAMIDINE™, and/or ATOVAQUONE™ to prophylactically treat or prevent an opportunistic *Pneumocystis carinii* pneumonia infection. In

15 another specific embodiment, Therapeutics of the invention are used in any combination with ISONIAZID™, RIFAMPIN™, PYRAZINAMIDE™, and/or ETHAMBUTOL™ to prophylactically treat or prevent an opportunistic *Mycobacterium avium* complex infection. In another specific embodiment, Therapeutics of the invention are used in any combination with RIFABUTIN™,

20 CLARITHROMYCIN™, and/or AZITHROMYCIN™ to prophylactically treat or prevent an opportunistic *Mycobacterium tuberculosis* infection. In another specific embodiment, Therapeutics of the invention are used in any combination with GANCICLOVIR™, FOSCARNET™, and/or CIDOFOVIR™ to prophylactically treat or prevent an opportunistic cytomegalovirus infection. In another specific

25 embodiment, Therapeutics of the invention are used in any combination with FLUCONAZOLE™, ITRACONAZOLE™, and/or KETOCONAZOLE™ to prophylactically treat or prevent an opportunistic fungal infection. In another specific embodiment, Therapeutics of the invention are used in any combination with ACYCLOVIR™ and/or FAMCICOLVIR™ to prophylactically treat or prevent an

30 opportunistic herpes simplex virus type I and/or type II infection. In another specific embodiment, Therapeutics of the invention are used in any combination with

PYRIMETHAMINE™ and/or LEUCOVORIN™ to prophylactically treat or prevent an opportunistic *Toxoplasma gondii* infection. In another specific embodiment, Therapeutics of the invention are used in any combination with LEUCOVORIN™ and/or NEUPOGEN™ to prophylactically treat or prevent an opportunistic bacterial
5 infection.

In a further embodiment, the Therapeutics of the invention are administered in combination with an antibiotic agent. Antibiotic agents that may be administered with the Therapeutics of the invention include, but are not limited to, amoxicillin, beta-lactamases, aminoglycosides, beta-lactam (glycopeptide), beta-lactamases,
10 Clindamycin, chloramphenicol, cephalosporins, ciprofloxacin, erythromycin, fluoroquinolones, macrolides, metronidazole, penicillins, quinolones, rapamycin, rifampin, streptomycin, sulfonamide, tetracyclines, trimethoprim, trimethoprim-sulfamethoxazole, and vancomycin.

In other embodiments, Therapeutics of the invention are administered in
15 combination with immunosuppressive agents. Immunosuppressive agents that may be administered in combination with the Therapeutics of the invention include, but are not limited to, steroids, cyclosporine, cyclosporine analogs, cyclophosphamide methylprednisone, prednisone, azathioprine, FK-506, 15-deoxyspergualin, and other immunosuppressive agents that act by suppressing the function of responding T cells.
20 Other immunosuppressive agents that may be administered in combination with the Therapeutics of the invention include, but are not limited to, prednisolone, methotrexate, thalidomide, methoxsalen, rapamycin, leflunomide, mizoribine (BREDININ™), brequinar, deoxyspergualin, and azaspirane (SKF 105685), ORTHOCLONE OKT® 3 (muromonab-CD3), SANDIMMUNE™, NEORAL™,
25 SANGDYA™ (cyclosporine), PROGRAF® (FK506, tacrolimus), CELLCEPT® (mycophenolate mofetil, of which the active metabolite is mycophenolic acid), IMURAN™ (azathioprine), glucocorticosteroids, adrenocortical steroids such as DELTASONE™ (prednisone) and HYDELTRASOL™ (prednisolone), FOLEX™ and MEXATE™ (methotrxate), OXSORALEN-ULTRA™ (methoxsalen) and
30 RAPAMUNE™ (sirolimus). In a specific embodiment, immunosuppressants may be used to prevent rejection of organ or bone marrow transplantation.

In an additional embodiment, Therapeutics of the invention are administered alone or in combination with one or more intravenous immune globulin preparations. Intravenous immune globulin preparations that may be administered with the Therapeutics of the invention include, but not limited to, GAMMAR™, IVEEGAM™, SANDOGLOBULIN™, GAMMAGARD S/D™, ATGAM™ (antithymocyte globulin), and GAMMUNE™. In a specific embodiment, Therapeutics of the invention are administered in combination with intravenous immune globulin preparations in transplantation therapy (e.g., bone marrow transplant).

10 In certain embodiments, the Therapeutics of the invention are administered alone or in combination with an anti-inflammatory agent. Anti-inflammatory agents that may be administered with the Therapeutics of the invention include, but are not limited to, corticosteroids (e.g. betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, and triamcinolone), nonsteroidal anti-inflammatory drugs (e.g., diclofenac, diflunisal, 15 etodolac, fenoprofen, floctafenine, flurbiprofen, ibuprofen, indomethacin, ketoprofen, meclofenamate, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, phenylbutazone, piroxicam, sulindac, tenoxicam, tiaprofenic acid, and tolmetin.), as well as antihistamines, aminoarylcarboxylic acid derivatives, arylacetic acid 20 derivatives, arylbutyric acid derivatives, arylcarboxylic acids, arylpropionic acid derivatives, pyrazoles, pyrazolones, salicylic acid derivatives, thiazinecarboxamides, e-acetamidocaproic acid, S-adenosylmethionine, 3-amino-4-hydroxybutyric acid, amixetrine, bendazac, benzydamine, bucolome, difenpiramide, ditazol, emorfazone, guaiazulene, nabumetone, nimesulide, orgotein, oxaceprol, paranyline, perisoxal, 25 pifoxime, proquazone, proxazole, and tenidap.

In an additional embodiment, the compositions of the invention are administered alone or in combination with an anti-angiogenic agent. Anti-angiogenic agents that may be administered with the compositions of the invention include, but are not limited to, Angiostatin (Entremed, Rockville, MD), Troponin-1 (Boston Life 30 Sciences, Boston, MA), anti-Invasive Factor, retinoic acid and derivatives thereof, paclitaxel (Taxol), Suramin, Tissue Inhibitor of Metalloproteinase-1, Tissue Inhibitor

of Metalloproteinase-2, VEGI, Plasminogen Activator Inhibitor-1, Plasminogen Activator Inhibitor-2, and various forms of the lighter "d group" transition metals.

Lighter "d group" transition metals include, for example, vanadium, molybdenum, tungsten, titanium, niobium, and tantalum species. Such transition metal species may form transition metal complexes. Suitable complexes of the above-mentioned transition metal species include oxo transition metal complexes.

Representative examples of vanadium complexes include oxo vanadium complexes such as vanadate and vanadyl complexes. Suitable vanadate complexes include metavanadate and orthovanadate complexes such as, for example, ammonium metavanadate, sodium metavanadate, and sodium orthovanadate. Suitable vanadyl complexes include, for example, vanadyl acetylacetonate and vanadyl sulfate including vanadyl sulfate hydrates such as vanadyl sulfate mono- and trihydrates.

Representative examples of tungsten and molybdenum complexes also include oxo complexes. Suitable oxo tungsten complexes include tungstate and tungsten oxide complexes. Suitable tungstate complexes include ammonium tungstate, calcium tungstate, sodium tungstate dihydrate, and tungstic acid. Suitable tungsten oxides include tungsten (IV) oxide and tungsten (VI) oxide. Suitable oxo molybdenum complexes include molybdate, molybdenum oxide, and molybdenyl complexes. Suitable molybdate complexes include ammonium molybdate and its hydrates, sodium molybdate and its hydrates, and potassium molybdate and its hydrates. Suitable molybdenum oxides include molybdenum (VI) oxide, molybdenum (VI) oxide, and molybdic acid. Suitable molybdenyl complexes include, for example, molybdenyl acetylacetonate. Other suitable tungsten and molybdenum complexes include hydroxo derivatives derived from, for example, glycerol, tartaric acid, and sugars.

A wide variety of other anti-angiogenic factors may also be utilized within the context of the present invention. Representative examples include, but are not limited to, platelet factor 4; protamine sulphate; sulphated chitin derivatives (prepared from queen crab shells), (Murata et al., Cancer Res. 51:22-26, (1991)); Sulphated Polysaccharide Peptidoglycan Complex (SP- PG) (the function of this compound may be enhanced by the presence of steroids such as estrogen, and tamoxifen citrate); Staurosporine; modulators of matrix metabolism, including for example, proline

analogues, L-hydroxyproline, D,L-3,4-dihydroxyproline, Thioproline, alpha,alpha-dipyridyl, aminopropionitrile fumarate; 4-propyl-5-(4-pyridinyl)-2(3H)-oxazolone; Methotrexate; Mitoxantrone; Heparin; Interferons; 2 Macroglobulin-serum; ChIMP-3 (Pavloff et al., *J. Bio. Chem.* 267:17321-17326, (1992)); Chymostatin (Tomkinson et al., *Biochem J.* 286:475-480, (1992)); Cyclodextrin Tetradecasulfate; Eponemycin; Camptothecin; Fumagillin (Ingber et al., *Nature* 348:555-557, (1990)); Gold Sodium Thiomalate ("GST"; Matsubara and Ziff, *J. Clin. Invest.* 79:1440-1446, (1987)); anticollagenase-serum; alpha2-antiplasmin (Holmes et al., *J. Biol. Chem.* 262(4):1659-1664, (1987)); Bisantrone (National Cancer Institute); Lobenzarit disodium (N-(2)-carboxyphenyl-4-chloroanthronilic acid disodium or "CCA"; (Takeuchi et al., *Agents Actions* 36:312-316, (1992)); and metalloproteinase inhibitors such as BB94.

Additional anti-angiogenic factors that may also be utilized within the context of the present invention include Thalidomide, (Celgene, Warren, NJ); Angiostatic steroid; AGM-1470 (H. Brem and J. Folkman *J. Pediatr. Surg.* 28:445-51 (1993)); an integrin alpha v beta 3 antagonist (C. Storgard et al., *J. Clin. Invest.* 103:47-54 (1999)); carboxynaminimidazole; Carboxyamidotriazole (CAI) (National Cancer Institute, Bethesda, MD); Conbretastatin A-4 (CA4P) (OXiGENE, Boston, MA); Squalamine (Magainin Pharmaceuticals, Plymouth Meeting, PA); TNP-470, (Tap Pharmaceuticals, Deerfield, IL); ZD-0101 AstraZeneca (London, UK); APRA (CT2584); Benefin, Byrostatin-1 (SC339555); CGP-41251 (PKC 412); CM101; Dexrazoxane (ICRF187); DMXAA; Endostatin; Flavopridiol; Genestein; GTE; ImmTher; Iressa (ZD1839); Octreotide (Somatostatin); Panretin; Penacillamine; Photopoint; PI-88; Prinomastat (AG-3340) Purlytin; Suradista (FCE26644); Tamoxifen (Nolvadex); Tazarotene; Tetrathiomolybdate; Xeloda (Capecitabine); and 5-Fluorouracil.

Anti-angiogenic agents that may be administered in combination with the compounds of the invention may work through a variety of mechanisms including, but not limited to, inhibiting proteolysis of the extracellular matrix, blocking the function of endothelial cell-extracellular matrix adhesion molecules, by antagonizing the function of angiogenesis inducers such as growth factors, and inhibiting integrin receptors expressed on proliferating endothelial cells. Examples of anti-angiogenic

inhibitors that interfere with extracellular matrix proteolysis and which may be administered in combination with the compositions of the invention include, but are not limited to, AG-3340 (Agouron, La Jolla, CA), BAY-12-9566 (Bayer, West Haven, CT), BMS-275291 (Bristol Myers Squibb, Princeton, NJ), CGS-27032A (Novartis, East Hanover, NJ), Marimastat (British Biotech, Oxford, UK), and Metastat (Aeterna, St-Foy, Quebec). Examples of anti-angiogenic inhibitors that act by blocking the function of endothelial cell-extracellular matrix adhesion molecules and which may be administered in combination with the compositions of the invention include, but are not limited to, EMD-121974 (Merck KgaA Darmstadt, Germany) and Vitaxin (Ixsys, La Jolla, CA/Medimmune, Gaithersburg, MD). Examples of anti-angiogenic agents that act by directly antagonizing or inhibiting angiogenesis inducers and which may be administered in combination with the compositions of the invention include, but are not limited to, Angiozyme (Ribozyme, Boulder, CO), Anti-VEGF antibody (Genentech, S. San Francisco, CA), PTK-787/ZK-225846 (Novartis, Basel, Switzerland), SU-101 (Sugen, S. San Francisco, CA), SU-5416 (Sugen/ Pharmacia Upjohn, Bridgewater, NJ), and SU-6668 (Sugen). Other anti-angiogenic agents act to indirectly inhibit angiogenesis. Examples of indirect inhibitors of angiogenesis which may be administered in combination with the compositions of the invention include, but are not limited to, IM-862 (Cytran, Kirkland, WA), Interferon-alpha, IL-12 (Roche, Nutley, NJ), and Pentosan polysulfate (Georgetown University, Washington, DC).

In particular embodiments, the use of compositions of the invention in combination with anti-angiogenic agents is contemplated for the treatment, prevention, and/or amelioration of an autoimmune disease, such as for example, an autoimmune disease described herein.

In a particular embodiment, the use of compositions of the invention in combination with anti-angiogenic agents is contemplated for the treatment, prevention, and/or amelioration of arthritis. In a more particular embodiment, the use of compositions of the invention in combination with anti-angiogenic agents is contemplated for the treatment, prevention, and/or amelioration of rheumatoid arthritis.

In another embodiment, the polynucleotides encoding a polypeptide of the present invention are administered in combination with an angiogenic protein, or polynucleotides encoding an angiogenic protein. Examples of angiogenic proteins that may be administered with the compositions of the invention include, but are not limited to, acidic and basic fibroblast growth factors, VEGF-1, VEGF-2, VEGF-3, epidermal growth factor alpha and beta, platelet-derived endothelial cell growth factor, platelet-derived growth factor, tumor necrosis factor alpha, hepatocyte growth factor, insulin-like growth factor, colony stimulating factor, macrophage colony stimulating factor, granulocyte/macrophage colony stimulating factor, and nitric oxide synthase.

In additional embodiments, compositions of the invention are administered in combination with a chemotherapeutic agent. Chemotherapeutic agents that may be administered with the Therapeutics of the invention include, but are not limited to alkylating agents such as nitrogen mustards (for example, Mechlorethamine, cyclophosphamide, Cyclophosphamide Ifosfamide, Melphalan (L-sarcosylsin), and Chlorambucil), ethylenimines and methylmelamines (for example, Hexamethylmelamine and Thiotepa), alkyl sulfonates (for example, Busulfan), nitrosoureas (for example, Carmustine (BCNU), Lomustine (CCNU), Semustine (methyl-CCNU), and Streptozocin (streptozotocin)), triazenes (for example, Dacarbazine (DTIC; dimethyltriazenoimidazolecarboxamide)), folic acid analogs (for example, Methotrexate (amethopterin)), pyrimidine analogs (for example, Fluorouracil (5-fluorouracil; 5-FU), Floxuridine (fluorodeoxyuridine; FudR), and Cytarabine (cytosine arabinoside)), purine analogs and related inhibitors (for example, Mercaptopurine (6-mercaptopurine; 6-MP), Thioguanine (6-thioguanine; TG), and Pentostatin (2'-deoxycoformycin)), vinca alkaloids (for example, Vinblastine (VLB, vinblastine sulfate)) and Vincristine (vincristine sulfate)), epipodophyllotoxins (for example, Etoposide and Teniposide), antibiotics (for example, Dactinomycin (actinomycin D), Daunorubicin (daunomycin; rubidomycin), Doxorubicin, Bleomycin, Plicamycin (mithramycin), and Mitomycin (mitomycin C)), enzymes (for example, L-Asparaginase), biological response modifiers (for example, Interferon-alpha and interferon-alpha-2b), platinum coordination compounds (for example, Cisplatin (cis-DDP) and Carboplatin), anthracenedione (Mitoxantrone),

substituted ureas (for example, Hydroxyurea), methylhydrazine derivatives (for example, Procarbazine (N-methylhydrazine; MIH), adrenocorticosteroids (for example, Prednisone), progestins (for example, Hydroxyprogesterone caproate, Medroxyprogesterone, Medroxyprogesterone acetate, and Megestrol acetate),
5 estrogens (for example, Diethylstilbestrol (DES), Diethylstilbestrol diphosphate, Estradiol, and Ethinyl estradiol), antiestrogens (for example, Tamoxifen), androgens (Testosterone propionate, and Fluoxymesterone), antiandrogens (for example, Flutamide), gonadotropin-releasing hormone analogs (for example, Leuprolide), other hormones and hormone analogs (for example, methyltestosterone, estramustine,
10 estramustine phosphate sodium, chlorotrianisene, and testolactone), and others (for example, dicarbazine, glutamic acid, and mitotane).

In one embodiment, the compositions of the invention are administered in combination with one or more of the following drugs: infliximab (also known as Remicade™ Centocor, Inc.), Trocade (Roche, RO-32-3555), Leflunomide (also
15 known as Arava™ from Hoechst Marion Roussel), Kineret™ (an IL-1 Receptor antagonist also known as Anakinra from Amgen, Inc.)

In a specific embodiment, compositions of the invention are administered in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or combination of one or more of the components of CHOP. In one
20 embodiment, the compositions of the invention are administered in combination with anti-CD20 antibodies, human monoclonal anti-CD20 antibodies. In another embodiment, the compositions of the invention are administered in combination with anti-CD20 antibodies and CHOP, or anti-CD20 antibodies and any combination of one or more of the components of CHOP, particularly cyclophosphamide and/or
25 prednisone. In a specific embodiment, compositions of the invention are administered in combination with Rituximab. In a further embodiment, compositions of the invention are administered with Rituximab and CHOP, or Rituximab and any combination of one or more of the components of CHOP, particularly cyclophosphamide and/or prednisone. In a specific embodiment, compositions of the
30 invention are administered in combination with tositumomab. In a further embodiment, compositions of the invention are administered with tositumomab and CHOP, or tositumomab and any combination of one or more of the components of

CHOP, particularly cyclophosphamide and/or prednisone. The anti-CD20 antibodies may optionally be associated with radioisotopes, toxins or cytotoxic prodrugs.

In another specific embodiment, the compositions of the invention are administered in combination Zevalin™. In a further embodiment, compositions of the invention are administered with Zevalin™ and CHOP, or Zevalin™ and any combination of one or more of the components of CHOP, particularly cyclophosphamide and/or prednisone. Zevalin™ may be associated with one or more radisotopes. Particularly preferred isotopes are ⁹⁰Y and ¹¹¹In.

In an additional embodiment, the Therapeutics of the invention are administered in combination with cytokines. Cytokines that may be administered with the Therapeutics of the invention include, but are not limited to, IL2, IL3, IL4, IL5, IL6, IL7, IL10, IL12, IL13, IL15, anti-CD40, CD40L, IFN-gamma and TNF-alpha. In another embodiment, Therapeutics of the invention may be administered with any interleukin, including, but not limited to, IL-1alpha, IL-1beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-16, IL-17, IL-18, IL-19, IL-20, and IL-21.

In one embodiment, the Therapeutics of the invention are administered in combination with members of the TNF family. TNF, TNF-related or TNF-like molecules that may be administered with the Therapeutics of the invention include, but are not limited to, soluble forms of TNF-alpha, lymphotoxin-alpha (LT-alpha, also known as TNF-beta), LT-beta (found in complex heterotrimer LT-alpha2-beta), OPGL, FasL, CD27L, CD30L, CD40L, 4-1BBL, DcR3, OX40L, TNF-gamma (International Publication No. WO 96/14328), AIM-I (International Publication No. WO 97/33899), endokine-alpha (International Publication No. WO 98/07880), OPG, and neutrokin-alpha (International Publication No. WO 98/18921, OX40, and nerve growth factor (NGF), and soluble forms of Fas, CD30, CD27, CD40 and 4-IBB, TR2 (International Publication No. WO 96/34095), DR3 (International Publication No. WO 97/33904), DR4 (International Publication No. WO 98/32856), TR5 (International Publication No. WO 98/30693), TRANK, TR9 (International Publication No. WO 98/56892), TR10 (International Publication No. WO 98/54202), 312C2 (International Publication No. WO 98/06842), and TR12, and soluble forms CD154, CD70, and CD153.

In an additional embodiment, the Therapeutics of the invention are administered in combination with angiogenic proteins. Angiogenic proteins that may be administered with the Therapeutics of the invention include, but are not limited to, Glioma Derived Growth Factor (GDGF), as disclosed in European Patent Number
5 EP-399816; Platelet Derived Growth Factor-A (PDGF-A), as disclosed in European Patent Number EP-682110; Platelet Derived Growth Factor-B (PDGF-B), as disclosed in European Patent Number EP-282317; Placental Growth Factor (PIGF), as disclosed in International Publication Number WO 92/06194; Placental Growth Factor-2 (PIGF-2), as disclosed in Hauser et al., Growth Factors, 4:259-268 (1993);
10 Vascular Endothelial Growth Factor (VEGF), as disclosed in International Publication Number WO 90/13649; Vascular Endothelial Growth Factor-A (VEGF-A), as disclosed in European Patent Number EP-506477; Vascular Endothelial Growth Factor-2 (VEGF-2), as disclosed in International Publication Number WO 96/39515; Vascular Endothelial Growth Factor B (VEGF-3); Vascular Endothelial Growth
15 Factor B-186 (VEGF-B186), as disclosed in International Publication Number WO 96/26736; Vascular Endothelial Growth Factor-D (VEGF-D), as disclosed in International Publication Number WO 98/02543; Vascular Endothelial Growth Factor-D (VEGF-D), as disclosed in International Publication Number WO 98/07832; and Vascular Endothelial Growth Factor-E (VEGF-E), as disclosed in German Patent
20 Number DE19639601. The above mentioned references are herein incorporated by reference in their entireties.

In an additional embodiment, the Therapeutics of the invention are administered in combination with Fibroblast Growth Factors. Fibroblast Growth Factors that may be administered with the Therapeutics of the invention include, but
25 are not limited to, FGF-1, FGF-2, FGF-3, FGF-4, FGF-5, FGF-6, FGF-7, FGF-8, FGF-9, FGF-10, FGF-11, FGF-12, FGF-13, FGF-14, and FGF-15.

In an additional embodiment, the Therapeutics of the invention are administered in combination with hematopoietic growth factors. Hematopoietic growth factors that may be administered with the Therapeutics of the invention
30 include, but are not limited to, granulocyte macrophage colony stimulating factor (GM-CSF) (sargramostim, LEUKINE™, PROKINE™), granulocyte colony stimulating factor (G-CSF) (filgrastim, NEUPOGEN™), macrophage colony

stimulating factor (M-CSF, CSF-1) erythropoietin (epoetin alfa, EPOGEN™, PROCRIT™), stem cell factor (SCF, c-kit ligand, steel factor), megakaryocyte colony stimulating factor, PIXY321 (a GMCSF/IL-3 fusion protein), interleukins, especially any one or more of IL-1 through IL-12, interferon-gamma, or
5 thrombopoietin.

In certain embodiments, Therapeutics of the present invention are administered in combination with adrenergic blockers, such as, for example, acebutolol, atenolol, betaxolol, bisoprolol, carteolol, labetalol, metoprolol, nadolol, oxprenolol, penbutolol, pindolol, propranolol, sotalol, and timolol.

10 In another embodiment, the Therapeutics of the invention are administered in combination with an antiarrhythmic drug (e.g., adenosine, amiodarone, bretylium, digitalis, digoxin, digitoxin, diltiazem, disopyramide, esmolol, flecainide, lidocaine, mexiletine, moricizine, phenytoin, procainamide, N-acetyl procainamide, propafenone, propranolol, quinidine, sotalol, tocainide, and verapamil).

15 In another embodiment, the Therapeutics of the invention are administered in combination with diuretic agents, such as carbonic anhydrase-inhibiting agents (e.g., acetazolamide, dichlorophenamide, and methazolamide), osmotic diuretics (e.g., glycerin, isosorbide, mannitol, and urea), diuretics that inhibit $\text{Na}^+\text{-K}^+\text{-2Cl}^-$ symport (e.g., furosemide, bumetanide, azosemide, piretanide, triparamide, ethacrynic acid, 20 muzolimine, and torsemide), thiazide and thiazide-like diuretics (e.g., bendroflumethiazide, benzthiazide, chlorothiazide, hydrochlorothiazide, hydroflumethiazide, methyclothiazide, polythiazide, trichormethiazide, chlorthalidone, indapamide, metolazone, and quinethazone), potassium sparing diuretics (e.g., amiloride and triamterene), and mineralcorticoid receptor antagonists
25 (e.g., spironolactone, canrenone, and potassium canrenoate).

In one embodiment, the Therapeutics of the invention are administered in combination with treatments for endocrine and/or hormone imbalance disorders. Treatments for endocrine and/or hormone imbalance disorders include, but are not limited to, ^{127}I , radioactive isotopes of iodine such as ^{131}I and ^{123}I ; recombinant
30 growth hormone, such as HUMATROPE™ (recombinant somatropin); growth hormone analogs such as PROTROPIN™ (somatrem); dopamine agonists such as PARLODEL™ (bromocriptine); somatostatin analogs such as SANDOSTATIN™

(octreotide); gonadotropin preparations such as PREGNYL™, A.P.L.™ and PROFASI™ (chorionic gonadotropin (CG)), PERGONAL™ (menotropins), and METRODIN™ (urofollitropin (uFSH)); synthetic human gonadotropin releasing hormone preparations such as FACTREL™ and LUTREPULSE™ (gonadorelin hydrochloride); synthetic gonadotropin agonists such as LUPRON™ (leuprolide acetate), SUPPRELIN™ (histrelin acetate), SYNAREL™ (nafarelin acetate), and ZOLADEX™ (goserelin acetate); synthetic preparations of thyrotropin-releasing hormone such as RELEFACT TRH™ and THYPINONE™ (protirelin); recombinant human TSH such as THYROGEN™; synthetic preparations of the sodium salts of the natural isomers of thyroid hormones such as L-T₄™, SYNTHROID™ and LEVOTHROID™ (levothyroxine sodium), L-T₃™, CYTOMEL™ and TRIOSTAT™ (liothyroine sodium), and THYROLAR™ (liotrix); antithyroid compounds such as 6-*n*-propylthiouracil (propylthiouracil), 1-methyl-2-mercaptoimidazole and TAPAZOLE™ (methimazole), NEO-MERCAZOLE™ (carbimazole); beta-adrenergic receptor antagonists such as propranolol and esmolol; Ca²⁺ channel blockers; dexamethasone and iodinated radiological contrast agents such as TELEPAQUE™ (iopanoic acid) and ORAGRAFIN™ (sodium ipodate).

Additional treatments for endocrine and/or hormone imbalance disorders include, but are not limited to, estrogens or conjugated estrogens such as ESTRACE™ (estradiol), ESTINYL™ (ethinyl estradiol), PREMARIN™, ESTRATAB™, ORTHO-EST™, OGEN™ and estropipate (estrone), ESTROVIS™ (quinestrol), ESTRADERM™ (estradiol), DELESTROGEN™ and VALERGEN™ (estradiol valerate), DEPO-ESTRADIOL CYPIONATE™ and ESTROJECT LA™ (estradiol cypionate); antiestrogens such as NOLVADEX™ (tamoxifen), SEROPHENE™ and CLOMID™ (clomiphene); progestins such as DURALUTIN™ (hydroxyprogesterone caproate), MPA™ and DEPO-PROVERA™ (medroxyprogesterone acetate), PROVERA™ and CYCRIN™ (MPA), MEGACE™ (megestrol acetate), NORLUTIN™ (norethindrone), and NORLUTATE™ and AYGESTIN™ (norethindrone acetate); progesterone implants such as NORPLANT SYSTEM™ (subdermal implants of norgestrel); antiprogestins such as RU 486™

(mifepristone); hormonal contraceptives such as ENOVID™ (norethynodrel plus mestranol), PROGESTASERT™ (intrauterine device that releases progesterone), LOESTRIN™, BREVICON™, MODICON™, GENORA™, NELONA™, NORINYL™, OVACON-35™ and OVACON-50™ (ethinyl estradiol/norethindrone),
 5 LEVLEN™, NORDETTE™, TRI-LEVLEN™ and TRIPHASIL-21™ (ethinyl estradiol/levonorgestrel) LO/OVRAL™ and OVRAL™ (ethinyl estradiol/norgestrel), DEMULEN™ (ethinyl estradiol/ethynodiol diacetate), NORINYL™, ORTHO-NOVUM™, NORETHIN™, GENORA™, and NELOVA™ (norethindrone/mestranol), DESOGEN™ and ORTHO-CEPT™ (ethinyl estradiol/desogestrel), ORTHO-
 10 CYCLEN™ and ORTHO-TRICYCLEN™ (ethinyl estradiol/norgestimate), MICRONOR™ and NOR-QD™ (norethindrone), and OVRETTE™ (norgestrel).

Additional treatments for endocrine and/or hormone imbalance disorders include, but are not limited to, testosterone esters such as methenolone acetate and testosterone undecanoate; parenteral and oral androgens such as TESTOJECT-50™
 15 (testosterone), TESTEX™ (testosterone propionate), DELATESTRYL™ (testosterone enanthate), DEPO-TESTOSTERONE™ (testosterone cypionate), DANOCRINE™ (danazol), HALOTESTIN™ (fluoxymesterone), ORETON METHYL™, TESTRED™ and VIRILON™ (methyltestosterone), and OXANDRIN™ (oxandrolone); testosterone transdermal systems such as TESTODERM™; androgen receptor
 20 antagonist and 5-alpha-reductase inhibitors such as ANDROCUR™ (cyproterone acetate), EULEXIN™ (flutamide), and PROSCAR™ (finasteride); adrenocorticotrophic hormone preparations such as CORTROSYN™ (cosyntropin); adrenocortical steroids and their synthetic analogs such as ACLOVATE™ (acclometasone dipropionate), CYCLOCORT™ (amcinonide), BECLOVENT™ and VANCERIL™ (beclomethasone
 25 dipropionate), CELESTONE™ (betamethasone), BENISONE™ and UTICORT™ (betamethasone benzoate), DIPROSONE™ (betamethasone dipropionate), CELESTONE PHOSPHATE™ (betamethasone sodium phosphate), CELESTONE SOLUSPAN™ (betamethasone sodium phosphate and acetate), BETA-VAL™ and VALISONE™ (betamethasone valerate), TEMOVATE™ (clobetasol propionate),
 30 CLODERM™ (clocortolone pivalate), CORTEF™ and HYDROCORTONE™

(cortisol (hydrocortisone)), HYDROCORTONE ACETATE™ (cortisol (hydrocortisone) acetate), LOCOID™ (cortisol (hydrocortisone) butyrate), HYDROCORTONE PHOSPHATE™ (cortisol (hydrocortisone) sodium phosphate), A-HYDROCORT™ and SOLU CORTEF™ (cortisol (hydrocortisone) sodium succinate), WESTCORT™ (cortisol (hydrocortisone) valerate), CORTISONE ACETATE™ (cortisone acetate), DESOWEN™ and TRIDESILON™ (desonide), TOPICORT™ (desoximetasone), DECADRON™ (dexamethasone), DECADRON LA™ (dexamethasone acetate), DECADRON PHOSPHATE™ and HEXADROL PHOSPHATE™ (dexamethasone sodium phosphate), FLORONE™ and

10 MAXIFLOR™ (diflorasone diacetate), FLORINEF ACETATE™ (fludrocortisone acetate), AEROBID™ and NASALIDE™ (flunisolide), FLUONID™ and SYNALAR™ (fluocinolone acetonide), LIDEX™ (fluocinonide), FLUOR-OP™ and FML™ (fluorometholone), CORDRAN™ (flurandrenolide), HALOG™ (halcinonide), HMS LIZUIFILM™ (medrysone), MEDROL™ (methylprednisolone), DEPO-

15 MEDROL™ and MEDROL ACETATE™ (methylprednisolone acetate), A-METHAPRED™ and SOLUMEDROL™ (methylprednisolone sodium succinate), ELOCON™ (mometasone furoate), HALDRONE™ (paramethasone acetate), DELTA-CORTEF™ (prednisolone), ECONOPRED™ (prednisolone acetate), HYDELTRASOL™ (prednisolone sodium phosphate), HYDELTRA-T.B.A™

20 (prednisolone tebutate), DELTASONE™ (prednisone), ARISTOCORT™ and KENACORT™ (triamcinolone), KENALOG™ (triamcinolone acetonide), ARISTOCORT™ and KENACORT DIACETATE™ (triamcinolone diacetate), and ARISTOSPAN™ (triamcinolone hexacetonide); inhibitors of biosynthesis and action of adrenocortical steroids such as CYTADREN™ (aminoglutethimide), NIZORAL™

25 (ketoconazole), MODRASTANE™ (trilostane), and METOPIRONE™ (metyrapone).

Additional treatments for endocrine and/or hormone imbalance disorders include, but are not limited to bovine, porcine or human insulin or mixtures thereof; insulin analogs; recombinant human insulin such as HUMULIN™ and NOVOLIN™; oral hypoglycemic agents such as ORAMIDE™ and ORINASE™ (tolbutamide),

30 DIABINESE™ (chlorpropamide), TOLAMIDE™ and TOLINASE™ (tolazamide),

DYMELOSTM (acetohexamide), glibenclamide, MICRONASETM, DIBETATM and GLYNASETM (glyburide), GLUCOTROLTM (glipizide), and DIAMICRONTM (gliclazide), GLUCOPHAGETM (metformin), PRECOSETM (acarbose), AMARYLTM (glimepiride), and ciglitazone; thiazolidinediones (TZDs) such as rosiglitazone, AVANDIATM (rosiglitazone maleate) ACTOSTM (pioglitazone), and troglitazone; alpha-glucosidase inhibitors; bovine or porcine glucagon; somatostatins such as SANDOSTATINTM (octreotide); and diazoxides such as PROGLYCEMTM (diazoxide). In still other embodiments, Therapeutics of the invention are administered in combination with one or more of the following: a biguanide antidiabetic agent, a glitazone antidiabetic agent, and a sulfonylurea antidiabetic agent.

In one embodiment, the Therapeutics of the invention are administered in combination with treatments for uterine motility disorders. Treatments for uterine motility disorders include, but are not limited to, estrogen drugs such as conjugated estrogens (e.g., PREMARIN[®] and ESTRATAB[®]), estradiols (e.g., CLIMARA[®] and ALORA[®]), estropipate, and chlorotrianisene; progestin drugs (e.g., AMEN[®] (medroxyprogesterone), MICRONOR[®] (norethidrone acetate), PROMETRIUM[®] progesterone, and megestrol acetate); and estrogen/progesterone combination therapies such as, for example, conjugated estrogens/medroxyprogesterone (e.g., PREMPROTM and PREMPHASE[®]) and norethindrone acetate/ethinyl estradiol (e.g., FEMHRTTM).

In an additional embodiment, the Therapeutics of the invention are administered in combination with drugs effective in treating iron deficiency and hypochromic anemias, including but not limited to, ferrous sulfate (iron sulfate, FEOSOLTM), ferrous fumarate (e.g., FEOSTATTM), ferrous gluconate (e.g., FERGONTM), polysaccharide-iron complex (e.g., NIFEREXTM), iron dextran injection (e.g., INFEDTM), cupric sulfate, pyroxidine, riboflavin, Vitamin B₁₂, cyanocobalamin injection (e.g., REDISOLTM, RUBRAMIN PCTM), hydroxocobalamin, folic acid (e.g., FOLVITETM), leucovorin (folinic acid, 5-CHOH4PteGlu, citrovorum factor) or WELLCOVORIN (Calcium salt of leucovorin), transferrin or ferritin.

In certain embodiments, the Therapeutics of the invention are administered in combination with agents used to treat psychiatric disorders. Psychiatric drugs that may be administered with the Therapeutics of the invention include, but are not limited to, antipsychotic agents (e.g., chlorpromazine, chlorprothixene, clozapine, fluphenazine, haloperidol, loxapine, mesoridazine, molindone, olanzapine, 5 perphenazine, pimozide, quetiapine, risperidone, thioridazine, thiothixene, trifluoperazine, and triflupromazine), antimanic agents (e.g., carbamazepine, divalproex sodium, lithium carbonate, and lithium citrate), antidepressants (e.g., amitriptyline, amoxapine, bupropion, citalopram, clomipramine, desipramine, 10 doxepin, fluvoxamine, fluoxetine, imipramine, isocarboxazid, maprotiline, mirtazapine, nefazodone, nortriptyline, paroxetine, phenelzine, protriptyline, sertraline, tranylcypromine, trazodone, trimipramine, and venlafaxine), antianxiety agents (e.g., alprazolam, buspirone, chlordiazepoxide, clorazepate, diazepam, halazepam, lorazepam, oxazepam, and prazepam), and stimulants (e.g., d- 15 amphetamine, methylphenidate, and pemoline).

In other embodiments, the Therapeutics of the invention are administered in combination with agents used to treat neurological disorders. Neurological agents that may be administered with the Therapeutics of the invention include, but are not limited to, antiepileptic agents (e.g., carbamazepine, clonazepam, ethosuximide, 20 phenobarbital, phenytoin, primidone, valproic acid, divalproex sodium, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, zonisamide, diazepam, lorazepam, and clonazepam), antiparkinsonian agents (e.g., levodopa/carbidopa, selegiline, amantidine, bromocriptine, pergolide, ropinirole, pramipexole, benzotropine; biperiden; ethopropazine; procyclidine; trihexyphenidyl, 25 tolcapone), and ALS therapeutics (e.g. riluzole).

In another embodiment, Therapeutics of the invention are administered in combination with vasodilating agents and/or calcium channel blocking agents. Vasodilating agents that may be administered with the Therapeutics of the invention include, but are not limited to, Angiotensin Converting Enzyme (ACE) inhibitors 30 (e.g., papaverine, isoxsuprine, benazepril, captopril, cilazapril, enalapril, enalaprilat, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, spirapril, trandolapril, and nylidrin), and nitrates (e.g., isosorbide dinitrate, isosorbide mononitrate, and

nitroglycerin). Examples of calcium channel blocking agents that may be administered in combination with the Therapeutics of the invention include, but are not limited to amlodipine, bepridil, diltiazem, felodipine, flunarizine, isradipine, nicardipine, nifedipine, nimodipine, and verapamil.

- 5 In additional embodiments, the Therapeutics of the invention are administered in combination with other therapeutic or prophylactic regimens, such as, for example, radiation therapy.

Example 24: Method of Treating Decreased Levels of the Polypeptide

- 10 The present invention relates to a method for treating an individual in need of an increased level of a polypeptide of the invention in the body comprising administering to such an individual a composition comprising a therapeutically effective amount of an agonist of the invention (including polypeptides of the invention). Moreover, it will be appreciated that conditions caused by a decrease in
15 the standard or normal expression level of a secreted protein in an individual can be treated by administering the polypeptide of the present invention, preferably in the secreted form. Thus, the invention also provides a method of treatment of an individual in need of an increased level of the polypeptide comprising administering to such an individual a Therapeutic comprising an amount of the polypeptide to
20 increase the activity level of the polypeptide in such an individual.

For example, a patient with decreased levels of a polypeptide receives a daily dose 0.1-100 ug/kg of the polypeptide for six consecutive days. Preferably, the polypeptide is in the secreted form. The exact details of the dosing scheme, based on administration and formulation, are provided in Example 23.

25

Example 25: Method of Treating Increased Levels of the Polypeptide

- The present invention also relates to a method of treating an individual in need of a decreased level of a polypeptide of the invention in the body comprising administering to such an individual a composition comprising a therapeutically
30 effective amount of an antagonist of the invention (including polypeptides and antibodies of the invention).

In one example, antisense technology is used to inhibit production of a polypeptide of the present invention. This technology is one example of a method of decreasing levels of a polypeptide, preferably a secreted form, due to a variety of etiologies, such as cancer. For example, a patient diagnosed with abnormally increased levels of a polypeptide is administered intravenously antisense polynucleotides at 0.5, 1.0, 1.5, 2.0 and 3.0 mg/kg day for 21 days. This treatment is repeated after a 7-day rest period if the treatment was well tolerated. The formulation of the antisense polynucleotide is provided in Example 23.

10 **Example 26: Method of Treatment Using Gene Therapy-Ex Vivo**

One method of gene therapy transplants fibroblasts, which are capable of expressing a polypeptide, onto a patient. Generally, fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in tissue-culture medium and separated into small pieces. Small chunks of the tissue are placed on a wet surface of a tissue culture flask, approximately ten pieces are placed in each flask. The flask is turned upside down, closed tight and left at room temperature over night. After 24 hours at room temperature, the flask is inverted and the chunks of tissue remain fixed to the bottom of the flask and fresh media (e.g., Ham's F12 media, with 10% FBS, penicillin and streptomycin) is added. The flasks are then incubated at 37 degree C for approximately one week.

At this time, fresh media is added and subsequently changed every several days. After an additional two weeks in culture, a monolayer of fibroblasts emerge. The monolayer is trypsinized and scaled into larger flasks.

pMV-7 (Kirschmeier, P.T. et al., DNA, 7:219-25 (1988)), flanked by the long terminal repeats of the Moloney murine sarcoma virus, is digested with EcoRI and HindIII and subsequently treated with calf intestinal phosphatase. The linear vector is fractionated on agarose gel and purified, using glass beads.

The cDNA encoding a polypeptide of the present invention can be amplified using PCR primers which correspond to the 5' and 3' end sequences respectively as set forth in Example 1 using primers and having appropriate restriction sites and initiation/stop codons, if necessary. Preferably, the 5' primer contains an EcoRI site and the 3' primer includes a HindIII site. Equal quantities of the Moloney murine

sarcoma virus linear backbone and the amplified EcoRI and HindIII fragment are added together, in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The ligation mixture is then used to transform bacteria HB101, which are then plated onto
5 agar containing kanamycin for the purpose of confirming that the vector has the gene of interest properly inserted.

The amphotropic pA317 or GP+am12 packaging cells are grown in tissue culture to confluent density in Dulbecco's Modified Eagles Medium (DMEM) with 10% calf serum (CS), penicillin and streptomycin. The MSV vector containing the
10 gene is then added to the media and the packaging cells transduced with the vector. The packaging cells now produce infectious viral particles containing the gene (the packaging cells are now referred to as producer cells).

Fresh media is added to the transduced producer cells, and subsequently, the media is harvested from a 10 cm plate of confluent producer cells. The spent media,
15 containing the infectious viral particles, is filtered through a millipore filter to remove detached producer cells and this media is then used to infect fibroblast cells. Media is removed from a sub-confluent plate of fibroblasts and quickly replaced with the media from the producer cells. This media is removed and replaced with fresh media. If the titer of virus is high, then virtually all fibroblasts will be infected and no
20 selection is required. If the titer is very low, then it is necessary to use a retroviral vector that has a selectable marker, such as neo or his. Once the fibroblasts have been efficiently infected, the fibroblasts are analyzed to determine whether protein is produced.

The engineered fibroblasts are then transplanted onto the host, either alone or
25 after having been grown to confluence on cytodex 3 microcarrier beads.

Example 27: Gene Therapy Using Endogenous Genes Corresponding To Polynucleotides of the Invention

Another method of gene therapy according to the present invention involves
30 operably associating the endogenous polynucleotide sequence of the invention with a promoter via homologous recombination as described, for example, in U.S. Patent NO: 5,641,670, issued June 24, 1997; International Publication NO: WO 96/29411,

published September 26, 1996; International Publication NO: WO 94/12650, published August 4, 1994; Koller et al., *Proc. Natl. Acad. Sci. USA*, 86:8932-8935 (1989); and Zijlstra et al., *Nature*, 342:435-438 (1989). This method involves the activation of a gene which is present in the target cells, but which is not expressed in
5 the cells, or is expressed at a lower level than desired.

Polynucleotide constructs are made which contain a promoter and targeting sequences, which are homologous to the 5' non-coding sequence of endogenous polynucleotide sequence, flanking the promoter. The targeting sequence will be sufficiently near the 5' end of the polynucleotide sequence so the promoter will be
10 operably linked to the endogenous sequence upon homologous recombination. The promoter and the targeting sequences can be amplified using PCR. Preferably, the amplified promoter contains distinct restriction enzyme sites on the 5' and 3' ends. Preferably, the 3' end of the first targeting sequence contains the same restriction enzyme site as the 5' end of the amplified promoter and the 5' end of the second
15 targeting sequence contains the same restriction site as the 3' end of the amplified promoter.

The amplified promoter and the amplified targeting sequences are digested with the appropriate restriction enzymes and subsequently treated with calf intestinal phosphatase. The digested promoter and digested targeting sequences are added
20 together in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The construct is size fractionated on an agarose gel then purified by phenol extraction and ethanol precipitation.

In this Example, the polynucleotide constructs are administered as naked
25 polynucleotides via electroporation. However, the polynucleotide constructs may also be administered with transfection-facilitating agents, such as liposomes, viral sequences, viral particles, precipitating agents, etc. Such methods of delivery are known in the art.

Once the cells are transfected, homologous recombination will take place
30 which results in the promoter being operably linked to the endogenous polynucleotide sequence. This results in the expression of polynucleotide corresponding to the

polynucleotide in the cell. Expression may be detected by immunological staining, or any other method known in the art.

Fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in DMEM + 10% fetal calf serum. Exponentially growing or early stationary
5 phase fibroblasts are trypsinized and rinsed from the plastic surface with nutrient medium. An aliquot of the cell suspension is removed for counting, and the remaining cells are subjected to centrifugation. The supernatant is aspirated and the pellet is resuspended in 5 ml of electroporation buffer (20 mM HEPES pH 7.3, 137 mM NaCl, 5 mM KCl, 0.7 mM Na₂ HPO₄, 6 mM dextrose). The cells are recentrifuged, the
10 supernatant aspirated, and the cells resuspended in electroporation buffer containing 1 mg/ml acetylated bovine serum albumin. The final cell suspension contains approximately 3×10^6 cells/ml. Electroporation should be performed immediately following resuspension.

Plasmid DNA is prepared according to standard techniques. For example, to
15 construct a plasmid for targeting to the locus corresponding to the polynucleotide of the invention, plasmid pUC18 (MBI Fermentas, Amherst, NY) is digested with HindIII. The CMV promoter is amplified by PCR with an XbaI site on the 5' end and a BamHI site on the 3' end. Two non-coding sequences are amplified via PCR: one non-coding sequence (fragment 1) is amplified with a HindIII site at the 5' end and an
20 Xba site at the 3' end; the other non-coding sequence (fragment 2) is amplified with a BamHI site at the 5' end and a HindIII site at the 3' end. The CMV promoter and the fragments (1 and 2) are digested with the appropriate enzymes (CMV promoter - XbaI and BamHI; fragment 1 - XbaI; fragment 2 - BamHI) and ligated together. The resulting ligation product is digested with HindIII, and ligated with the HindIII-
25 digested pUC18 plasmid.

Plasmid DNA is added to a sterile cuvette with a 0.4 cm electrode gap (Bio-Rad). The final DNA concentration is generally at least 120 μ g/ml. 0.5 ml of the cell suspension (containing approximately 1.5×10^6 cells) is then added to the cuvette, and the cell suspension and DNA solutions are gently mixed. Electroporation is
30 performed with a Gene-Pulser apparatus (Bio-Rad). Capacitance and voltage are set at 960 μ F and 250-300 V, respectively. As voltage increases, cell survival decreases, but the percentage of surviving cells that stably incorporate the introduced DNA into their

genome increases dramatically. Given these parameters, a pulse time of approximately 14-20 mSec should be observed.

Electroporated cells are maintained at room temperature for approximately 5 min, and the contents of the cuvette are then gently removed with a sterile transfer
5 pipette. The cells are added directly to 10 ml of prewarmed nutrient media (DMEM with 15% calf serum) in a 10 cm dish and incubated at 37 degree C. The following day, the media is aspirated and replaced with 10 ml of fresh media and incubated for a further 16-24 hours.

The engineered fibroblasts are then injected into the host, either alone or after
10 having been grown to confluence on cytodex 3 microcarrier beads. The fibroblasts now produce the protein product. The fibroblasts can then be introduced into a patient as described above.

Example 28: Method of Treatment Using Gene Therapy - In Vivo

15 Another aspect of the present invention is using *in vivo* gene therapy methods to treat disorders, diseases and conditions. The gene therapy method relates to the introduction of naked nucleic acid (DNA, RNA, and antisense DNA or RNA) sequences into an animal to increase or decrease the expression of the polypeptide. The polynucleotide of the present invention may be operatively linked to a promoter
20 or any other genetic elements necessary for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques and methods are known in the art, see, for example, WO90/11092, WO98/11779; U.S. Patent NO. 5693622, 5705151, 5580859; Tabata et al., Cardiovasc. Res. 35(3):470-479 (1997); Chao et al., Pharmacol. Res. 35(6):517-522 (1997); Wolff, Neuromuscul. Disord. 7(5):314-318
25 (1997); Schwartz et al., Gene Ther. 3(5):405-411 (1996); Tsurumi et al., Circulation 94(12):3281-3290 (1996) (incorporated herein by reference).

The polynucleotide constructs may be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, intestine and the like). The
30 polynucleotide constructs can be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

The term "naked" polynucleotide, DNA or RNA, refers to sequences that are

free from any delivery vehicle that acts to assist, promote, or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the polynucleotides of the present invention may also be delivered in liposome formulations (such as those taught in

5 Felgner P.L. et al. (1995) Ann. NY Acad. Sci. 772:126-139 and Abdallah B. et al. (1995) Biol. Cell 85(1):1-7) which can be prepared by methods well known to those skilled in the art.

The polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain

10 sequences that allow for replication. Any strong promoter known to those skilled in the art can be used for driving the expression of DNA. Unlike other gene therapies techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to

15 provide production of the desired polypeptide for periods of up to six months.

The polynucleotide construct can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and

20 connective tissue. Interstitial space of the tissues comprises the intercellular fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of

25 the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely

30 differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. *In vivo* muscle cells are particularly competent in their ability to take up and express polynucleotides.

For the naked polynucleotide injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 g/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration. The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or mucous membranes of the nose. In addition, naked polynucleotide constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

The dose response effects of injected polynucleotide in muscle *in vivo* is determined as follows. Suitable template DNA for production of mRNA coding for polypeptide of the present invention is prepared in accordance with a standard recombinant DNA methodology. The template DNA, which may be either circular or linear, is either used as naked DNA or complexed with liposomes. The quadriceps muscles of mice are then injected with various amounts of the template DNA.

Five to six week old female and male Balb/C mice are anesthetized by intraperitoneal injection with 0.3 ml of 2.5% Avertin. A 1.5 cm incision is made on the anterior thigh, and the quadriceps muscle is directly visualized. The template DNA is injected in 0.1 ml of carrier in a 1 cc syringe through a 27 gauge needle over one minute, approximately 0.5 cm from the distal insertion site of the muscle into the knee and about 0.2 cm deep. A suture is placed over the injection site for future localization, and the skin is closed with stainless steel clips.

After an appropriate incubation time (e.g., 7 days) muscle extracts are prepared by excising the entire quadriceps. Every fifth 15 μ m cross-section of the individual quadriceps muscles is histochemically stained for protein expression. A time course for protein expression may be done in a similar fashion except that quadriceps from different mice are harvested at different times. Persistence of DNA in muscle following injection may be determined by Southern blot analysis after

preparing total cellular DNA and HIRT supernatants from injected and control mice. The results of the above experimentation in mice can be use to extrapolate proper dosages and other treatment parameters in humans and other animals using naked DNA.

5

Example 29: Transgenic Animals.

The polypeptides of the invention can also be expressed in transgenic animals. Animals of any species, including, but not limited to, mice, rats, rabbits, hamsters, guinea pigs, pigs, micro-pigs, goats, sheep, cows and non-human primates, *e.g.*, baboons, monkeys, and chimpanzees may be used to generate transgenic animals. In a specific embodiment, techniques described herein or otherwise known in the art, are used to express polypeptides of the invention in humans, as part of a gene therapy protocol.

Any technique known in the art may be used to introduce the transgene (i.e., polynucleotides of the invention) into animals to produce the founder lines of transgenic animals. Such techniques include, but are not limited to, pronuclear microinjection (Paterson et al., Appl. Microbiol. Biotechnol. 40:691-698 (1994); Carver et al., Biotechnology (NY) 11:1263-1270 (1993); Wright et al., Biotechnology (NY) 9:830-834 (1991); and Hoppe et al., U.S. Pat. No. 4,873,191 (1989)); retrovirus mediated gene transfer into germ lines (Van der Putten et al., Proc. Natl. Acad. Sci., USA 82:6148-6152 (1985)), blastocysts or embryos; gene targeting in embryonic stem cells (Thompson et al., Cell 56:313-321 (1989)); electroporation of cells or embryos (Lo, 1983, Mol Cell. Biol. 3:1803-1814 (1983)); introduction of the polynucleotides of the invention using a gene gun (see, e.g., Ulmer et al., Science 259:1745 (1993); introducing nucleic acid constructs into embryonic pleuripotent stem cells and transferring the stem cells back into the blastocyst; and sperm-mediated gene transfer (Lavitrano et al., Cell 57:717-723 (1989); etc. For a review of such techniques, see Gordon, "Transgenic Animals," Intl. Rev. Cytol. 115:171-229 (1989), which is incorporated by reference herein in its entirety.

Any technique known in the art may be used to produce transgenic clones containing polynucleotides of the invention, for example, nuclear transfer into enucleated oocytes of nuclei from cultured embryonic, fetal, or adult cells induced to

quiescence (Campell et al., Nature 380:64-66 (1996); Wilmut et al., Nature 385:810-813 (1997)).

The present invention provides for transgenic animals that carry the transgene in all their cells, as well as animals which carry the transgene in some, but not all their cells, *i.e.*, mosaic animals or chimeric. The transgene may be integrated as a single transgene or as multiple copies such as in concatamers, *e.g.*, head-to-head tandems or head-to-tail tandems. The transgene may also be selectively introduced into and activated in a particular cell type by following, for example, the teaching of Lasko et al. (Lasko et al., Proc. Natl. Acad. Sci. USA 89:6232-6236 (1992)). The regulatory sequences required for such a cell-type specific activation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art. When it is desired that the polynucleotide transgene be integrated into the chromosomal site of the endogenous gene, gene targeting is preferred. Briefly, when such a technique is to be utilized, vectors containing some nucleotide sequences homologous to the endogenous gene are designed for the purpose of integrating, via homologous recombination with chromosomal sequences, into and disrupting the function of the nucleotide sequence of the endogenous gene. The transgene may also be selectively introduced into a particular cell type, thus inactivating the endogenous gene in only that cell type, by following, for example, the teaching of Gu et al. (Gu et al., Science 265:103-106 (1994)). The regulatory sequences required for such a cell-type specific inactivation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art.

Once transgenic animals have been generated, the expression of the recombinant gene may be assayed utilizing standard techniques. Initial screening may be accomplished by Southern blot analysis or PCR techniques to analyze animal tissues to verify that integration of the transgene has taken place. The level of mRNA expression of the transgene in the tissues of the transgenic animals may also be assessed using techniques which include, but are not limited to, Northern blot analysis of tissue samples obtained from the animal, *in situ* hybridization analysis, and reverse transcriptase-PCR (rt-PCR). Samples of transgenic gene-expressing tissue may also be evaluated immunocytochemically or immunohistochemically using antibodies specific for the transgene product.

Once the founder animals are produced, they may be bred, inbred, outbred, or crossbred to produce colonies of the particular animal. Examples of such breeding strategies include, but are not limited to: outbreeding of founder animals with more than one integration site in order to establish separate lines; inbreeding of separate
5 lines in order to produce compound transgenics that express the transgene at higher levels because of the effects of additive expression of each transgene; crossing of heterozygous transgenic animals to produce animals homozygous for a given integration site in order to both augment expression and eliminate the need for screening of animals by DNA analysis; crossing of separate homozygous lines to
10 produce compound heterozygous or homozygous lines; and breeding to place the transgene on a distinct background that is appropriate for an experimental model of interest.

Transgenic animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of
15 polypeptides of the present invention, studying diseases, disorders, and/or conditions associated with aberrant expression, and in screening for compounds effective in ameliorating such diseases, disorders, and/or conditions.

Example 30: Knock-Out Animals.

20 Endogenous gene expression can also be reduced by inactivating or "knocking out" the gene and/or its promoter using targeted homologous recombination. (*E.g.*, see Smithies et al., *Nature* 317:230-234 (1985); Thomas & Capecchi, *Cell* 51:503-512 (1987); Thompson et al., *Cell* 5:313-321 (1989); each of which is incorporated by reference herein in its entirety). For example, a mutant, non-functional
25 polynucleotide of the invention (or a completely unrelated DNA sequence) flanked by DNA homologous to the endogenous polynucleotide sequence (either the coding regions or regulatory regions of the gene) can be used, with or without a selectable marker and/or a negative selectable marker, to transfect cells that express polypeptides of the invention *in vivo*. In another embodiment, techniques known in
30 the art are used to generate knockouts in cells that contain, but do not express the gene of interest. Insertion of the DNA construct, via targeted homologous recombination, results in inactivation of the targeted gene. Such approaches are particularly suited in

research and agricultural fields where modifications to embryonic stem cells can be used to generate animal offspring with an inactive targeted gene (*e.g.*, see Thomas & Capecchi 1987 and Thompson 1989, *supra*). However this approach can be routinely adapted for use in humans provided the recombinant DNA constructs are directly
5 administered or targeted to the required site *in vivo* using appropriate viral vectors that will be apparent to those of skill in the art.

In further embodiments of the invention, cells that are genetically engineered to express the polypeptides of the invention, or alternatively, that are genetically engineered not to express the polypeptides of the invention (*e.g.*, knockouts) are
10 administered to a patient *in vivo*. Such cells may be obtained from the patient (*i.e.*, animal, including human) or an MHC compatible donor and can include, but are not limited to fibroblasts, bone marrow cells, blood cells (*e.g.*, lymphocytes), adipocytes, muscle cells, endothelial cells etc. The cells are genetically engineered *in vitro* using recombinant DNA techniques to introduce the coding sequence of polypeptides of the
15 invention into the cells, or alternatively, to disrupt the coding sequence and/or endogenous regulatory sequence associated with the polypeptides of the invention, *e.g.*, by transduction (using viral vectors; and preferably vectors that integrate the transgene into the cell genome) or transfection procedures, including, but not limited to, the use of plasmids, cosmids, YACs, naked DNA, electroporation, liposomes, etc..
20 The coding sequence of the polypeptides of the invention can be placed under the control of a strong constitutive or inducible promoter or promoter/enhancer to achieve expression, and preferably secretion, of the polypeptides of the invention. The engineered cells which express and preferably secrete the polypeptides of the invention can be introduced into the patient systemically, *e.g.*, in the circulation, or
25 intraperitoneally.

Alternatively, the cells can be incorporated into a matrix and implanted in the body, *e.g.*, genetically engineered fibroblasts can be implanted as part of a skin graft; genetically engineered endothelial cells can be implanted as part of a lymphatic or vascular graft. (See, for example, Anderson et al. U.S. Patent No. 5,399,349; and
30 Mulligan & Wilson, U.S. Patent No. 5,460,959 each of which is incorporated by reference herein in its entirety).

When the cells to be administered are non-autologous or non-MHC compatible cells, they can be administered using well known techniques which prevent the development of a host immune response against the introduced cells. For example, the cells may be introduced in an encapsulated form which, while allowing
5 for an exchange of components with the immediate extracellular environment, does not allow the introduced cells to be recognized by the host immune system.

Transgenic and "knock-out" animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying diseases, disorders, and/or
10 conditions associated with aberrant expression, and in screening for compounds effective in ameliorating such diseases, disorders, and/or conditions.

Example 31: Production of an Antibody

Hybridoma Technology

15 The antibodies of the present invention can be prepared by a variety of methods. (See, Current Protocols, Chapter 2.) As one example of such methods, cells expressing polypeptide(s) of the invention are administered to an animal to induce the production of sera containing polyclonal antibodies. In a preferred method, a preparation of polypeptide(s) of the invention is prepared and purified to render it
20 substantially free of natural contaminants. Such a preparation is then introduced into an animal in order to produce polyclonal antisera of greater specific activity.

Monoclonal antibodies specific for polypeptide(s) of the invention are prepared using hybridoma technology. (Kohler et al., Nature 256:495 (1975); Kohler et al., Eur. J. Immunol. 6:511 (1976); Kohler et al., Eur. J. Immunol. 6:292 (1976);
25 Hammerling et al., in: Monoclonal Antibodies and T-Cell Hybridomas, Elsevier, N.Y., pp. 563-681 (1981)). In general, an animal (preferably a mouse) is immunized with polypeptide(s) of the invention, or, more preferably, with a secreted polypeptide-expressing cell. Such polypeptide-expressing cells are cultured in any suitable tissue culture medium, preferably in Earle's modified Eagle's medium supplemented with
30 10% fetal bovine serum (inactivated at about 56°C), and supplemented with about 10 g/l of nonessential amino acids, about 1,000 U/ml of penicillin, and about 100 µg/ml of streptomycin.

The splenocytes of such mice are extracted and fused with a suitable myeloma cell line. Any suitable myeloma cell line may be employed in accordance with the present invention; however, it is preferable to employ the parent myeloma cell line (SP2O), available from the ATCC. After fusion, the resulting hybridoma cells are
5 selectively maintained in HAT medium, and then cloned by limiting dilution as described by Wands et al. (Gastroenterology 80:225-232 (1981)). The hybridoma cells obtained through such a selection are then assayed to identify clones which secrete antibodies capable of binding the polypeptide(s) of the invention.

Alternatively, additional antibodies capable of binding polypeptide(s) of the
10 invention can be produced in a two-step procedure using anti-idiotypic antibodies. Such a method makes use of the fact that antibodies are themselves antigens, and therefore, it is possible to obtain an antibody which binds to a second antibody. In accordance with this method, protein specific antibodies are used to immunize an animal, preferably a mouse. The splenocytes of such an animal are then used to
15 produce hybridoma cells, and the hybridoma cells are screened to identify clones which produce an antibody whose ability to bind to the polypeptide(s) of the invention protein-specific antibody can be blocked by polypeptide(s) of the invention. Such antibodies comprise anti-idiotypic antibodies to the polypeptide(s) of the invention protein-specific antibody and are used to immunize an animal to induce
20 formation of further polypeptide(s) of the invention protein-specific antibodies.

For in vivo use of antibodies in humans, an antibody is "humanized". Such antibodies can be produced using genetic constructs derived from hybridoma cells producing the monoclonal antibodies described above. Methods for producing chimeric and humanized antibodies are known in the art and are discussed herein.
25 (See, for review, Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., WO 8702671; Boulianne et al., Nature 312:643 (1984); Neuberger et al., Nature 314:268 (1985).)

30

Isolation Of Antibody Fragments Directed polypeptide(s) of the invention From A Library Of scFvs

Naturally occurring V-genes isolated from human PBLs are constructed into a library of antibody fragments which contain reactivities against polypeptide(s) of the invention to which the donor may or may not have been exposed (see e.g., U.S. Patent 5,885,793 incorporated herein by reference in its entirety).

5 Rescue of the Library. A library of scFvs is constructed from the RNA of human PBLs as described in PCT publication WO 92/01047. To rescue phage displaying antibody fragments, approximately 10⁹ E. coli harboring the phagemid are used to inoculate 50 ml of 2xTY containing 1% glucose and 100 µg/ml of ampicillin (2xTY-AMP-GLU) and grown to an O.D. of 0.8 with shaking. Five ml of this culture
10 is used to inoculate 50 ml of 2xTY-AMP-GLU, 2 x 10⁸ TU of delta gene 3 helper (M13 delta gene III, see PCT publication WO 92/01047) are added and the culture incubated at 37°C for 45 minutes without shaking and then at 37°C for 45 minutes with shaking. The culture is centrifuged at 4000 r.p.m. for 10 min. and the pellet resuspended in 2 liters of 2xTY containing 100 µg/ml ampicillin and 50 µg/ml
15 kanamycin and grown overnight. Phage are prepared as described in PCT publication WO 92/01047.

M13 delta gene III is prepared as follows: M13 delta gene III helper phage does not encode gene III protein, hence the phage(mid) displaying antibody fragments have a greater avidity of binding to antigen. Infectious M13 delta gene III
20 particles are made by growing the helper phage in cells harboring a pUC19 derivative supplying the wild type gene III protein during phage morphogenesis. The culture is incubated for 1 hour at 37° C without shaking and then for a further hour at 37°C with shaking. Cells are spun down (IEC-Centra 8,400 r.p.m. for 10 min), resuspended in 300 ml 2xTY broth containing 100 µg ampicillin/ml and 25 µg kanamycin/ml (2xTY-
25 AMP-KAN) and grown overnight, shaking at 37°C. Phage particles are purified and concentrated from the culture medium by two PEG-precipitations (Sambrook et al., 1990), resuspended in 2 ml PBS and passed through a 0.45 µm filter (Minisart NML; Sartorius) to give a final concentration of approximately 10¹³ transducing units/ml (ampicillin-resistant clones).

30 Panning of the Library. Immunotubes (Nunc) are coated overnight in PBS with 4 ml of either 100 µg/ml or 10 µg/ml of a polypeptide of the present invention. Tubes are blocked with 2% Marvel-PBS for 2 hours at 37°C and then washed 3 times

in PBS. Approximately 10¹³ TU of phage is applied to the tube and incubated for 30 minutes at room temperature tumbling on an over and under turntable and then left to stand for another 1.5 hours. Tubes are washed 10 times with PBS 0.1% Tween-20 and 10 times with PBS. Phage are eluted by adding 1 ml of 100 mM triethylamine and rotating 15 minutes on an under and over turntable after which the solution is immediately neutralized with 0.5 ml of 1.0M Tris-HCl, pH 7.4. Phage are then used to infect 10 ml of mid-log E. coli TG1 by incubating eluted phage with bacteria for 30 minutes at 37°C. The E. coli are then plated on TYE plates containing 1% glucose and 100 µg/ml ampicillin. The resulting bacterial library is then rescued with delta gene 3 helper phage as described above to prepare phage for a subsequent round of selection. This process is then repeated for a total of 4 rounds of affinity purification with tube-washing increased to 20 times with PBS, 0.1% Tween-20 and 20 times with PBS for rounds 3 and 4.

Characterization of Binders. Eluted phage from the 3rd and 4th rounds of selection are used to infect E. coli HB 2151 and soluble scFv is produced (Marks, et al., 1991) from single colonies for assay. ELISAs are performed with microtitre plates coated with either 10 pg/ml of the polypeptide of the present invention in 50 mM bicarbonate pH 9.6. Clones positive in ELISA are further characterized by PCR fingerprinting (see, e.g., PCT publication WO 92/01047) and then by sequencing. These ELISA positive clones may also be further characterized by techniques known in the art, such as, for example, epitope mapping, binding affinity, receptor signal transduction, ability to block or competitively inhibit antibody/antigen binding, and competitive agonistic or antagonistic activity.

Example 32: Assays Detecting Stimulation or Inhibition of B cell Proliferation and Differentiation

Generation of functional humoral immune responses requires both soluble and cognate signaling between B-lineage cells and their microenvironment. Signals may impart a positive stimulus that allows a B-lineage cell to continue its programmed development, or a negative stimulus that instructs the cell to arrest its current developmental pathway. To date, numerous stimulatory and inhibitory signals have been

found to influence B cell responsiveness including IL-2, IL-4, IL-5, IL-6, IL-7, IL10, IL-13, IL-14 and IL-15. Interestingly, these signals are by themselves weak effectors but can, in combination with various co-stimulatory proteins, induce activation, proliferation, differentiation, homing, tolerance and death among B cell populations.

- 5 One of the best studied classes of B-cell co-stimulatory proteins is the TNF-superfamily. Within this family CD40, CD27, and CD30 along with their respective ligands CD154, CD70, and CD153 have been found to regulate a variety of immune responses. Assays which allow for the detection and/or observation of the proliferation and differentiation of these B-cell populations and their precursors are valuable tools in
- 10 determining the effects various proteins may have on these B-cell populations in terms of proliferation and differentiation. Listed below are two assays designed to allow for the detection of the differentiation, proliferation, or inhibition of B-cell populations and their precursors.

- In Vitro Assay- Purified polypeptides of the invention, or truncated forms
- 15 thereof, is assessed for its ability to induce activation, proliferation, differentiation or inhibition and/or death in B-cell populations and their precursors. The activity of the polypeptides of the invention on purified human tonsillar B cells, measured qualitatively over the dose range from 0.1 to 10,000 ng/mL, is assessed in a standard B-lymphocyte co-stimulation assay in which purified tonsillar B cells are cultured in
- 20 the presence of either formalin-fixed Staphylococcus aureus Cowan I (SAC) or immobilized anti-human IgM antibody as the priming agent. Second signals such as IL-2 and IL-15 synergize with SAC and IgM crosslinking to elicit B cell proliferation as measured by tritiated-thymidine incorporation. Novel synergizing agents can be readily identified using this assay. The assay involves isolating human tonsillar B
- 25 cells by magnetic bead (MACS) depletion of CD3-positive cells. The resulting cell population is greater than 95% B cells as assessed by expression of CD45R(B220).

- Various dilutions of each sample are placed into individual wells of a 96-well plate to which are added 10^5 B-cells suspended in culture medium (RPMI 1640 containing 10% FBS, 5×10^{-5} M 2ME, 100U/ml penicillin, 10ug/ml streptomycin, and 10^{-5} dilution of
- 30 SAC) in a total volume of 150ul. Proliferation or inhibition is quantitated by a 20h pulse (1uCi/well) with 3 H-thymidine (6.7 Ci/mM) beginning 72h post factor addition. The positive and negative controls are IL2 and medium respectively.

In Vivo Assay- BALB/c mice are injected (i.p.) twice per day with buffer only, or 2 mg/Kg of a polypeptide of the invention, or truncated forms thereof. Mice receive this treatment for 4 consecutive days, at which time they are sacrificed and various tissues and serum collected for analyses. Comparison of H&E sections from normal spleens and spleens treated with polypeptides of the invention identify the results of the activity of the polypeptides on spleen cells, such as the diffusion of peri-arterial lymphatic sheaths, and/or significant increases in the nucleated cellularity of the red pulp regions, which may indicate the activation of the differentiation and proliferation of B-cell populations. Immunohistochemical studies using a B cell marker, anti-CD45R(B220), are used to determine whether any physiological changes to splenic cells, such as splenic disorganization, are due to increased B-cell representation within loosely defined B-cell zones that infiltrate established T-cell regions.

Flow cytometric analyses of the spleens from mice treated with polypeptide is used to indicate whether the polypeptide specifically increases the proportion of ThB+, CD45R(B220)dull B cells over that which is observed in control mice.

Likewise, a predicted consequence of increased mature B-cell representation in vivo is a relative increase in serum Ig titers. Accordingly, serum IgM and IgA levels are compared between buffer and polypeptide-treated mice.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides of the invention (e.g., gene therapy), agonists, and/or antagonists of polynucleotides or polypeptides of the invention.

Example 33: T Cell Proliferation Assay

Proliferation assay for Resting PBLs.

A CD3-induced proliferation assay is performed on PBMCs and is measured by the uptake of ^3H -thymidine. The assay is performed as follows. Ninety-six well plates are coated with 100 microliters per well of mAb to CD3 (HIT3a, Pharmingen) or isotype-matched control mAb (B33.1) overnight at 4°C (1 microgram/ml in .05M bicarbonate buffer, pH 9.5), then washed three times with PBS. PBMC are isolated by F/H gradient centrifugation from human peripheral blood and added to quadruplicate wells (5×10^4 /well) of mAb coated plates in RPMI containing

10% FCS and P/S in the presence of varying concentrations of TNF Delta and/or TNF Epsilon protein (total volume 200 microliters). Relevant protein buffer and medium alone are controls. After 48 hr. culture at 37°C, plates are spun for 2 min. at 1000 rpm and 100 microliters of supernatant is removed and stored -20°C for measurement of IL-2 (or other cytokines) if effect on proliferation is observed. Wells are supplemented with 100 microliters of medium containing 0.5 microcuries of ³H-thymidine and cultured at 37°C for 18-24 hr. Wells are harvested and incorporation of ³H-thymidine used as a measure of proliferation. Anti-CD3 alone is the positive control for proliferation. IL-2 (100 U/ml) is also used as a control which enhances proliferation. Control antibody which does not induce proliferation of T cells is used as the negative controls for the effects of TNF Delta and/or TNF Epsilon proteins.

Alternatively, a proliferation assay on resting PBL (peripheral blood lymphocytes) is measured by the up-take of ³H-thymidine. The assay is performed as follows. PBMC are isolated by Ficoll (LSM, ICN Biotechnologies, Aurora, Ohio) gradient centrifugation from human peripheral blood, and are cultured overnight in 10% (Fetal Calf Serum, Biofluids, Rockville, MD)/RPMI (Gibco BRL, Gaithersburg, MD). This overnight incubation period allows the adherent cells to attach to the plastic, which results in a lower background in the assay as there are fewer cells that can act as antigen presenting cells or that might be producing growth factors. The following day the non-adherent cells are collected, washed and used in the proliferation assay. The assay is performed in a 96 well plate using 2 x 10⁴ cells/well in a final volume of 200 microliters. The supernatants (e.g., CHO or 293T supernatants) expressing the protein of interest are tested at a 30% final dilution, therefore 60ul are added to 140ul of 10% FCS/RPMI containing the cells. Control supernatants are used at the same final dilution and express the following proteins: vector (negative control), IL-2 (*), IFN γ , TNF α , IL-10 and TR2. In addition to the control supernatants, recombinant human IL-2 (R & D Systems, Minneapolis, MN) at a final concentration of 100ng/ml is also used. After 24 hours of culture, each well is pulsed with 1uCi of ³H-thymidine (Nen, Boston, MA). Cells are then harvested 20 hours following pulsing and incorporation of ³H-thymidine is used as a measure of proliferation. Results are expressed as an average of triplicate samples plus or minus standard error.

(*) The amount of the control cytokines IL-2, IFN γ , TNF α and IL-10 produced in each transfection varies between 300pg to 5ng/ml.

Costimulation assay.

5 A costimulation assay on resting PBL (peripheral blood lymphocytes) is performed in the presence of immobilized antibodies to CD3 and CD28. The use of antibodies specific for the invariant regions of CD3 mimic the induction of T cell activation that would occur through stimulation of the T cell receptor by an antigen. Cross-linking of the TCR (first signal) in the absence of a costimulatory signal
10 (second signal) causes very low induction of proliferation and will eventually result in a state of "anergy", which is characterized by the absence of growth and inability to produce cytokines. The addition of a costimulatory signal such as an antibody to CD28, which mimics the action of the costimulatory molecule. B7-1 expressed on activated APCs, results in enhancement of T cell responses including cell survival and
15 production of IL-2. Therefore this type of assay allows to detect both positive and negative effects caused by addition of supernatants expressing the proteins of interest on T cell proliferation.

The assay is performed as follows. Ninety-six well plates are coated with 100ng/ml anti-CD3 and 5ug/ml anti-CD28 (Pharmingen, San Diego, CA) in a final
20 volume of 100ul and incubated overnight at 4C. Plates are washed twice with PBS before use. PBMC are isolated by Ficoll (LSM, ICN Biotechnologies, Aurora, Ohio) gradient centrifugation from human peripheral blood, and are cultured overnight in 10% FCS(Fetal Calf Serum, Biofluids, Rockville, MD)/RPMI (Gibco BRL, Gaithersburg, MD). This overnight incubation period allows the adherent cells to
25 attach to the plastic, which results in a lower background in the assay as there are fewer cells that can act as antigen presenting cells or that might be producing growth factors. The following day the non adherent cells are collected, washed and used in the proliferation assay. The assay is performed in a 96 well plate using 2×10^4 cells/well in a final volume of 200ul. The supernatants (e.g., CHO or 293T
30 supernatants) expressing the protein of interest are tested at a 30% final dilution, therefore 60ul are added to 140ul of 10% FCS/RPMI containing the cells. Control supernatants are used at the same final dilution and express the following proteins:

vector only (negative control), IL-2, IFN γ , TNF α , IL-10 and TR2. In addition to the control supernatants recombinant human IL-2 (R & D Systems, Minneapolis, MN) at a final concentration of 10ng/ml is also used. After 24 hours of culture, each well is pulsed with 1uCi of ^3H -thymidine (Nen, Boston, MA). Cells are then harvested 20
5 hours following pulsing and incorporation of ^3H -thymidine is used as a measure of proliferation. Results are expressed as an average of triplicate samples plus or minus standard error.

Costimulation assay: IFN γ and IL-2 ELISA.

10 The assay is performed as follows. Twenty-four well plates are coated with either 300ng/ml or 600ng/ml anti-CD3 and 5ug/ml anti-CD28 (Pharmingen, San Diego, CA) in a final volume of 500ul and incubated overnight at 4C. Plates are washed twice with PBS before use. PBMC are isolated by Ficoll (LSM, ICN Biotechnologies, Aurora, Ohio) gradient centrifugation from human peripheral blood,
15 and are cultured overnight in 10% FCS(Fetal Calf Serum, Biofluids, Rockville, MD)/RPMI (Gibco BRL, Gaithersburg, MD). This overnight incubation period allows the adherent cells to attach to the plastic, which results in a lower background in the assay as there are fewer cells that can act as antigen presenting cells or that might be producing growth factors. The following day the non adherent cells are
20 collected, washed and used in the costimulation assay. The assay is performed in the pre-coated twenty-four well plate using 1×10^5 cells/well in a final volume of 900ul. The supernatants (293T supernatants) expressing the protein of interest are tested at a 30% final dilution, therefore 300ul are added to 600ul of 10% FCS/RPMI containing the cells. Control supernatants are used at the same final dilution and express the
25 following proteins: vector only(negative control), IL-2, IFN γ , IL-12 and IL-18. In addition to the control supernatants recombinant human IL-2 (all cytokines were purchased from R & D Systems, Minneapolis, MN) at a final concentration of 10ng/ml, IL-12 at a final concentration of 1ng/ml and IL-18 at a final concentration of 50ng/ml are also used. Controls and unknown samples are tested in duplicate.
30 Supernatant samples (250ul) are collected 2 days and 5 days after the beginning of the assay. ELISAs to test for IFN γ and IL-2 secretion are performed using kits

purchased from R & D Systems, (Minneapolis, MN). Results are expressed as an average of duplicate samples plus or minus standard error.

Proliferation assay for preactivated-resting T cells.

5 A proliferation assay on preactivated-resting T cells is performed on cells that are previously activated with the lectin phytohemagglutinin (PHA). Lectins are polymeric plant proteins that can bind to residues on T cell surface glycoproteins including the TCR and act as polyclonal activators. PBLs treated with PHA and then cultured in the presence of low doses of IL-2 resemble effector T cells. These cells
10 are generally more sensitive to further activation induced by growth factors such as IL-2. This is due to the expression of high affinity IL-2 receptors that allows this population to respond to amounts of IL-2 that are 100 fold lower than what would have an effect on a naïve T cell. Therefore the use of this type of cells might enable to detect the effect of very low doses of an unknown growth factor, that would not be
15 sufficient to induce proliferation on resting (naïve) T cells.

The assay is performed as follows. PBMC are isolated by F/H gradient centrifugation from human peripheral blood, and are cultured in 10% FCS (Fetal Calf Serum, Biofluids, Rockville, MD)/RPMI (Gibco BRL, Gaithersburg, MD) in the presence of 2 µg/ml PHA (Sigma, Saint Louis, MO) for three days. The cells are then
20 washed in PBS and cultured in 10% FCS/RPMI in the presence of 5 ng/ml of human recombinant IL-2 (R & D Systems, Minneapolis, MN) for 3 days. The cells are washed and rested in starvation medium (1% FCS/RPMI) for 16 hours prior to the beginning of the proliferation assay. An aliquot of the cells is analyzed by FACS to determine the percentage of T cells (CD3 positive cells) present; this usually ranges
25 between 93-97% depending on the donor. The assay is performed in a 96 well plate using 2×10^4 cells/well in a final volume of 200 µl. The supernatants (e.g., CHO or 293T supernatants) expressing the protein of interest are tested at a 30% final dilution, therefore 60 µl are added to 140 µl of 10% FCS/RPMI containing the cells. Control supernatants are used at the same final dilution and express the following proteins:
30 vector (negative control), IL-2, IFN γ , TNF α , IL-10 and TR2. In addition to the control supernatants recombinant human IL-2 at a final concentration of 10 ng/ml is also used. After 24 hours of culture, each well is pulsed with 1 µCi of ^3H -

thymidine(Nen, Boston, MA). Cells are then harvested 20 hours following pulsing and incorporation of ^3H -thymidine is used as a measure of proliferation. Results are expressed as an average of triplicate samples plus or minus standard error.

The studies described in this example test activity of polypeptides of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides of the invention (e.g., gene therapy), agonists, and/or antagonists of polynucleotides or polypeptides of the invention.

Example 34: Effect of Polypeptides of the Invention on the Expression of MHC Class II, Costimulatory and Adhesion Molecules and Cell Differentiation of Monocytes and Monocyte-Derived Human Dendritic Cells

Dendritic cells are generated by the expansion of proliferating precursors found in the peripheral blood: adherent PBMC or elutriated monocytic fractions are cultured for 7-10 days with GM-CSF (50 ng/ml) and IL-4 (20 ng/ml). These dendritic cells have the characteristic phenotype of immature cells (expression of CD1, CD80, CD86, CD40 and MHC class II antigens). Treatment with activating factors, such as TNF- α , causes a rapid change in surface phenotype (increased expression of MHC class I and II, costimulatory and adhesion molecules, downregulation of FC γ RII, upregulation of CD83). These changes correlate with increased antigen-presenting capacity and with functional maturation of the dendritic cells.

FACS analysis of surface antigens is performed as follows. Cells are treated 1-3 days with increasing concentrations of polypeptides of the invention or LPS (positive control), washed with PBS containing 1% BSA and 0.02 mM sodium azide, and then incubated with 1:20 dilution of appropriate FITC- or PE-labeled monoclonal antibodies for 30 minutes at 4 degrees C. After an additional wash, the labeled cells are analyzed by flow cytometry on a FACScan (Becton Dickinson).

Effect on the production of cytokines. Cytokines generated by dendritic cells, in particular IL-12, are important in the initiation of T-cell dependent immune responses. IL-12 strongly influences the development of Th1 helper T-cell immune response, and induces cytotoxic T and NK cell function. An ELISA is used to

measure the IL-12 release as follows. Dendritic cells ($10^6/\text{ml}$) are treated with increasing concentrations of polypeptides of the invention for 24 hours. LPS (100 ng/ml) is added to the cell culture as positive control. Supernatants from the cell cultures are then collected and analyzed for IL-12 content using commercial ELISA kit (e.g., R & D Systems (Minneapolis, MN)). The standard protocols provided with the kits are used.

Effect on the expression of MHC Class II, costimulatory and adhesion molecules. Three major families of cell surface antigens can be identified on monocytes: adhesion molecules, molecules involved in antigen presentation, and Fc receptor. Modulation of the expression of MHC class II antigens and other costimulatory molecules, such as B7 and ICAM-1, may result in changes in the antigen presenting capacity of monocytes and ability to induce T cell activation. Increase expression of Fc receptors may correlate with improved monocyte cytotoxic activity, cytokine release and phagocytosis.

FACS analysis is used to examine the surface antigens as follows. Monocytes are treated 1-5 days with increasing concentrations of polypeptides of the invention or LPS (positive control), washed with PBS containing 1% BSA and 0.02 mM sodium azide, and then incubated with 1:20 dilution of appropriate FITC- or PE-labeled monoclonal antibodies for 30 minutes at 4 degreesC. After an additional wash, the labeled cells are analyzed by flow cytometry on a FACScan (Becton Dickinson).

Monocyte activation and/or increased survival. Assays for molecules that activate (or alternatively, inactivate) monocytes and/or increase monocyte survival (or alternatively, decrease monocyte survival) are known in the art and may routinely be applied to determine whether a molecule of the invention functions as an inhibitor or activator of monocytes. Polypeptides, agonists, or antagonists of the invention can be screened using the three assays described below. For each of these assays, Peripheral blood mononuclear cells (PBMC) are purified from single donor leukopacks (American Red Cross, Baltimore, MD) by centrifugation through a Histopaque gradient (Sigma). Monocytes are isolated from PBMC by counterflow centrifugal elutriation.

Monocyte Survival Assay. Human peripheral blood monocytes progressively lose viability when cultured in absence of serum or other stimuli. Their death results from internally regulated process (apoptosis). Addition to the culture of activating factors, such as TNF-alpha dramatically improves cell survival and prevents DNA fragmentation. Propidium iodide (PI) staining is used to measure apoptosis as follows. Monocytes are cultured for 48 hours in polypropylene tubes in serum-free medium (positive control), in the presence of 100 ng/ml TNF-alpha (negative control), and in the presence of varying concentrations of the compound to be tested. Cells are suspended at a concentration of 2×10^6 /ml in PBS containing PI at a final concentration of 5 μ g/ml, and then incubated at room temperature for 5 minutes before FACSscan analysis. PI uptake has been demonstrated to correlate with DNA fragmentation in this experimental paradigm.

Effect on cytokine release. An important function of monocytes/macrophages is their regulatory activity on other cellular populations of the immune system through the release of cytokines after stimulation. An ELISA to measure cytokine release is performed as follows. Human monocytes are incubated at a density of 5×10^5 cells/ml with increasing concentrations of the a polypeptide of the invention and under the same conditions, but in the absence of the polypeptide. For IL-12 production, the cells are primed overnight with IFN (100 U/ml) in presence of a polypeptide of the invention. LPS (10 ng/ml) is then added. Conditioned media are collected after 24h and kept frozen until use. Measurement of TNF-alpha, IL-10, MCP-1 and IL-8 is then performed using a commercially available ELISA kit (e.g., R & D Systems (Minneapolis, MN)) and applying the standard protocols provided with the kit.

Oxidative burst. Purified monocytes are plated in 96-w plate at 2×10^5 cell/well. Increasing concentrations of polypeptides of the invention are added to the wells in a total volume of 0.2 ml culture medium (RPMI 1640 + 10% FCS, glutamine and antibiotics). After 3 days incubation, the plates are centrifuged and the medium is removed from the wells. To the macrophage monolayers, 0.2 ml per well of phenol red solution (140 mM NaCl, 10 mM potassium phosphate buffer pH 7.0, 5.5 mM

dextrose, 0.56 mM phenol red and 19 U/ml of HRPO) is added, together with the stimulant (200 nM PMA). The plates are incubated at 37°C for 2 hours and the reaction is stopped by adding 20 μ l 1N NaOH per well. The absorbance is read at 610 nm. To calculate the amount of H₂O₂ produced by the macrophages, a standard curve of a H₂O₂ solution of known molarity is performed for each experiment.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polypeptides, polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

Example 35: Biological Effects of Polypeptides of the Invention

Astrocyte and Neuronal Assays

Recombinant polypeptides of the invention, expressed in *Escherichia coli* and purified as described above, can be tested for activity in promoting the survival, neurite outgrowth, or phenotypic differentiation of cortical neuronal cells and for inducing the proliferation of glial fibrillary acidic protein immunopositive cells, astrocytes. The selection of cortical cells for the bioassay is based on the prevalent expression of FGF-1 and FGF-2 in cortical structures and on the previously reported enhancement of cortical neuronal survival resulting from FGF-2 treatment. A thymidine incorporation assay, for example, can be used to elucidate a polypeptide of the invention's activity on these cells.

Moreover, previous reports describing the biological effects of FGF-2 (basic FGF) on cortical or hippocampal neurons *in vitro* have demonstrated increases in both neuron survival and neurite outgrowth (Walicke et al., "Fibroblast growth factor promotes survival of dissociated hippocampal neurons and enhances neurite extension." *Proc. Natl. Acad. Sci. USA* 83:3012-3016. (1986), assay herein incorporated by reference in its entirety). However, reports from experiments done on PC-12 cells suggest that these two responses are not necessarily synonymous and may depend on not only which FGF is being tested but also on which receptor(s) are expressed on the target cells. Using the primary cortical neuronal culture paradigm, the ability of a polypeptide of the invention to

induce neurite outgrowth can be compared to the response achieved with FGF-2 using, for example, a thymidine incorporation assay.

Fibroblast and endothelial cell assays

5 Human lung fibroblasts are obtained from Clonetics (San Diego, CA) and maintained in growth media from Clonetics. Dermal microvascular endothelial cells are obtained from Cell Applications (San Diego, CA). For proliferation assays, the human lung fibroblasts and dermal microvascular endothelial cells can be cultured at 5,000 cells/well in a 96-well plate for one day in growth medium. The cells are then incubated
10 for one day in 0.1% BSA basal medium. After replacing the medium with fresh 0.1% BSA medium, the cells are incubated with the test proteins for 3 days. Alamar Blue (Alamar Biosciences, Sacramento, CA) is added to each well to a final concentration of 10%. The cells are incubated for 4 hr. Cell viability is measured by reading in a CytoFluor fluorescence reader. For the PGE₂ assays, the human lung fibroblasts are cultured at
15 5,000 cells/well in a 96-well plate for one day. After a medium change to 0.1% BSA basal medium, the cells are incubated with FGF-2 or polypeptides of the invention with or without IL-1 α for 24 hours. The supernatants are collected and assayed for PGE₂ by EIA kit (Cayman, Ann Arbor, MI). For the IL-6 assays, the human lung fibroblasts are cultured at 5,000 cells/well in a 96-well plate for one day. After a medium change to
20 0.1% BSA basal medium, the cells are incubated with FGF-2 or with or without polypeptides of the invention IL-1 α for 24 hours. The supernatants are collected and assayed for IL-6 by ELISA kit (Endogen, Cambridge, MA).

Human lung fibroblasts are cultured with FGF-2 or polypeptides of the invention for 3 days in basal medium before the addition of Alamar Blue to assess effects on growth
25 of the fibroblasts. FGF-2 should show a stimulation at 10 - 2500 ng/ml which can be used to compare stimulation with polypeptides of the invention.

Parkinson Models.

The loss of motor function in Parkinson's disease is attributed to a deficiency of
30 striatal dopamine resulting from the degeneration of the nigrostriatal dopaminergic

projection neurons. An animal model for Parkinson's that has been extensively characterized involves the systemic administration of 1-methyl-4 phenyl 1,2,3,6-tetrahydropyridine (MPTP). In the CNS, MPTP is taken-up by astrocytes and catabolized by monoamine oxidase B to 1-methyl-4-phenyl pyridine (MPP⁺) and released.

5 Subsequently, MPP⁺ is actively accumulated in dopaminergic neurons by the high-affinity reuptake transporter for dopamine. MPP⁺ is then concentrated in mitochondria by the electrochemical gradient and selectively inhibits nicotinamide adenine disphosphate: ubiquinone oxidoreductionase (complex I), thereby interfering with electron transport and eventually generating oxygen radicals.

10 It has been demonstrated in tissue culture paradigms that FGF-2 (basic FGF) has trophic activity towards nigral dopaminergic neurons (Ferrari et al., Dev. Biol. 1989). Recently, Dr. Unsicker's group has demonstrated that administering FGF-2 in gel foam implants in the striatum results in the near complete protection of nigral dopaminergic neurons from the toxicity associated with MPTP exposure (Otto and Unsicker, J.
15 Neuroscience, 1990).

Based on the data with FGF-2, polypeptides of the invention can be evaluated to determine whether it has an action similar to that of FGF-2 in enhancing dopaminergic neuronal survival *in vitro* and it can also be tested *in vivo* for protection of dopaminergic neurons in the striatum from the damage associated with MPTP treatment. The potential
20 effect of a polypeptide of the invention is first examined *in vitro* in a dopaminergic neuronal cell culture paradigm. The cultures are prepared by dissecting the midbrain floor plate from gestation day 14 Wistar rat embryos. The tissue is dissociated with trypsin and seeded at a density of 200,000 cells/cm² on polyorthinine-laminin coated glass coverslips. The cells are maintained in Dulbecco's Modified Eagle's medium and F12 medium
25 containing hormonal supplements (N1). The cultures are fixed with paraformaldehyde after 8 days *in vitro* and are processed for tyrosine hydroxylase, a specific marker for dopaminergic neurons, immunohistochemical staining. Dissociated cell cultures are prepared from embryonic rats. The culture medium is changed every third day and the factors are also added at that time.

30 Since the dopaminergic neurons are isolated from animals at gestation day 14, a developmental time which is past the stage when the dopaminergic precursor cells are proliferating, an increase in the number of tyrosine hydroxylase immunopositive neurons

would represent an increase in the number of dopaminergic neurons surviving *in vitro*. Therefore, if a polypeptide of the invention acts to prolong the survival of dopaminergic neurons, it would suggest that the polypeptide may be involved in Parkinson's Disease.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

Example 36: The Effect of Polypeptides of the Invention on the Growth of Vascular Endothelial Cells

On day 1, human umbilical vein endothelial cells (HUVEC) are seeded at $2-5 \times 10^4$ cells/35 mm dish density in M199 medium containing 4% fetal bovine serum (FBS), 16 units/ml heparin, and 50 units/ml endothelial cell growth supplements (ECGS, Biotechnology, Inc.). On day 2, the medium is replaced with M199 containing 10% FBS, 8 units/ml heparin. A polypeptide having the amino acid sequence of SEQ ID NO:Y, and positive controls, such as VEGF and basic FGF (bFGF) are added, at varying concentrations. On days 4 and 6, the medium is replaced. On day 8, cell number is determined with a Coulter Counter.

An increase in the number of HUVEC cells indicates that the polypeptide of the invention may proliferate vascular endothelial cells.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

Example 37: Stimulatory Effect of Polypeptides of the Invention on the Proliferation of Vascular Endothelial Cells

For evaluation of mitogenic activity of growth factors, the colorimetric MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)2H-tetrazolium) assay with the electron coupling reagent PMS (phenazine methosulfate) was

performed (CellTiter 96 AQ, Promega). Cells are seeded in a 96-well plate (5,000 cells/well) in 0.1 mL serum-supplemented medium and are allowed to attach overnight. After serum-starvation for 12 hours in 0.5% FBS, conditions (bFGF, VEGF₁₆₅ or a polypeptide of the invention in 0.5% FBS) with or without Heparin (8 U/ml) are added to wells for 48 hours. 20 mg of MTS/PMS mixture (1:0.05) are added per well and allowed to incubate for 1 hour at 37°C before measuring the absorbance at 490 nm in an ELISA plate reader. Background absorbance from control wells (some media, no cells) is subtracted, and seven wells are performed in parallel for each condition. See, Leak *et al. In Vitro Cell. Dev. Biol.* 30A:512-518 (1994).

10 The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

15 **Example 38: Inhibition of PDGF-induced Vascular Smooth Muscle Cell Proliferation Stimulatory Effect**

HAoSMC proliferation can be measured, for example, by BrdUrd incorporation. Briefly, subconfluent, quiescent cells grown on the 4-chamber slides are transfected with CRP or FITC-labeled AT2-3LP. Then, the cells are pulsed with 10% calf serum and 6 mg/ml BrdUrd. After 24 h, immunocytochemistry is performed by using BrdUrd Staining Kit (Zymed Laboratories). In brief, the cells are incubated with the biotinylated mouse anti-BrdUrd antibody at 4 degrees C for 2 h after being exposed to denaturing solution and then incubated with the streptavidin-peroxidase and diaminobenzidine. After counterstaining with hematoxylin, the cells are mounted for microscopic examination, and the BrdUrd-positive cells are counted. The BrdUrd index is calculated as a percent of the BrdUrd-positive cells to the total cell number. In addition, the simultaneous detection of the BrdUrd staining (nucleus) and the FITC uptake (cytoplasm) is performed for individual cells by the concomitant use of bright field illumination and dark field-UV fluorescent illumination. See, Hayashida et al., *J. Biol. Chem.* 6:271(36):21985-21992 (1996).

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

5

Example 39: Stimulation of Endothelial Migration

This example will be used to explore the possibility that a polypeptide of the invention may stimulate lymphatic endothelial cell migration.

10 Endothelial cell migration assays are performed using a 48 well microchemotaxis chamber (Neuroprobe Inc., Cabin John, MD; Falk, W., et al., J. Immunological Methods 1980;33:239-247). Polyvinylpyrrolidone-free polycarbonate filters with a pore size of 8 um (Nucleopore Corp. Cambridge, MA) are coated with 0.1% gelatin for at least 6 hours at room temperature and dried under sterile air. Test substances are diluted to appropriate
15 concentrations in M199 supplemented with 0.25% bovine serum albumin (BSA), and 25 ul of the final dilution is placed in the lower chamber of the modified Boyden apparatus. Subconfluent, early passage (2-6) HUVEC or BMEC cultures are washed and trypsinized for the minimum time required to achieve cell detachment. After placing the filter between lower and upper chamber, 2.5×10^5 cells suspended in 50 ul M199 containing 1%
20 FBS are seeded in the upper compartment. The apparatus is then incubated for 5 hours at 37°C in a humidified chamber with 5% CO₂ to allow cell migration. After the incubation period, the filter is removed and the upper side of the filter with the non-migrated cells is scraped with a rubber policeman. The filters are fixed with methanol and stained with a Giemsa solution (Diff-Quick, Baxter, McGraw Park, IL). Migration is quantified by
25 counting cells of three random high-power fields (40x) in each well, and all groups are performed in quadruplicate.

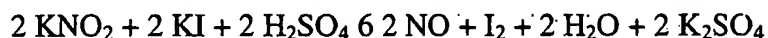
30 The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

Example 40: Stimulation of Nitric Oxide Production by Endothelial Cells

Nitric oxide released by the vascular endothelium is believed to be a mediator of vascular endothelium relaxation. Thus, activity of a polypeptide of the invention can be
 5 assayed by determining nitric oxide production by endothelial cells in response to the polypeptide.

Nitric oxide is measured in 96-well plates of confluent microvascular endothelial cells after 24 hours starvation and a subsequent 4 hr exposure to various levels of a positive control (such as VEGF-1) and the polypeptide of the invention. Nitric oxide in
 10 the medium is determined by use of the Griess reagent to measure total nitrite after reduction of nitric oxide-derived nitrate by nitrate reductase. The effect of the polypeptide of the invention on nitric oxide release is examined on HUVEC.

Briefly, NO release from cultured HUVEC monolayer is measured with a NO-specific polarographic electrode connected to a NO meter (Iso-NO, World Precision
 15 Instruments Inc.) (1049). Calibration of the NO elements is performed according to the following equation:



The standard calibration curve is obtained by adding graded concentrations of KNO_2 (0, 5, 10, 25, 50, 100, 250, and 500 nmol/L) into the calibration solution containing
 20 KI and H_2SO_4 . The specificity of the Iso-NO electrode to NO is previously determined by measurement of NO from authentic NO gas (1050). The culture medium is removed and HUVECs are washed twice with Dulbecco's phosphate buffered saline. The cells are then bathed in 5 ml of filtered Krebs-Henseleit solution in 6-well plates, and the cell plates are kept on a slide warmer (Lab Line Instruments Inc.) To maintain the temperature at 37°C.
 25 The NO sensor probe is inserted vertically into the wells, keeping the tip of the electrode 2 mm under the surface of the solution, before addition of the different conditions. S-nitroso acetyl penicillamin (SNAP) is used as a positive control. The amount of released NO is expressed as picomoles per 1×10^6 endothelial cells. All values reported are means of four to six measurements in each group (number of cell culture wells). See,
 30 Leak *et al. Biochem. and Biophys. Res. Comm.* 217:96-105 (1995).

The studies described in this example tested activity of polypeptides of the invention. However, one skilled in the art could easily modify the exemplified studies to

test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

Example 41: Effect of Polypeptides of the Invention on Cord Formation in

Angiogenesis

Another step in angiogenesis is cord formation, marked by differentiation of endothelial cells. This bioassay measures the ability of microvascular endothelial cells to form capillary-like structures (hollow structures) when cultured *in vitro*.

10 CADMEC (microvascular endothelial cells) are purchased from Cell Applications, Inc. as proliferating (passage 2) cells and are cultured in Cell Applications' CADMEC Growth Medium and used at passage 5. For the *in vitro* angiogenesis assay, the wells of a 48-well cell culture plate are coated with Cell Applications' Attachment Factor Medium (200 µl/well) for 30 min. at 37°C. CADMEC are seeded onto the coated wells at 7,500
15 cells/well and cultured overnight in Growth Medium. The Growth Medium is then replaced with 300 µg Cell Applications' Chord Formation Medium containing control buffer or a polypeptide of the invention (0.1 to 100 ng/ml) and the cells are cultured for an additional 48 hr. The numbers and lengths of the capillary-like chords are quantitated through use of the Boeckeler VIA-170 video image analyzer. All assays are done in
20 triplicate.

Commercial (R&D) VEGF (50 ng/ml) is used as a positive control. b-esteradiol (1 ng/ml) is used as a negative control. The appropriate buffer (without protein) is also utilized as a control.

The studies described in this example tested activity of a polypeptide of the
25 invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

Example 42: Angiogenic Effect on Chick Chorioallantoic Membrane

30

Chick chorioallantoic membrane (CAM) is a well-established system to examine angiogenesis. Blood vessel formation on CAM is easily visible and quantifiable. The

ability of polypeptides of the invention to stimulate angiogenesis in CAM can be examined.

Fertilized eggs of the White Leghorn chick (*Gallus gallus*) and the Japanese quail (*Coturnix coturnix*) are incubated at 37.8°C and 80% humidity. Differentiated CAM of
5 16-day-old chick and 13-day-old quail embryos is studied with the following methods.

On Day 4 of development, a window is made into the egg shell of chick eggs. The embryos are checked for normal development and the eggs sealed with cellotape. They are further incubated until Day 13. Thermanox coverslips (Nunc, Naperville, IL) are cut into disks of about 5 mm in diameter. Sterile and salt-free growth factors are dissolved in
10 distilled water and about 3.3 mg/ 5 ml are pipetted on the disks. After air-drying, the inverted disks are applied on CAM. After 3 days, the specimens are fixed in 3% glutaraldehyde and 2% formaldehyde and rinsed in 0.12 M sodium cacodylate buffer. They are photographed with a stereo microscope [Wild M8] and embedded for semi- and ultrathin sectioning as described above. Controls are performed with carrier disks alone.

15 The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

20 **Example 43: Angiogenesis Assay Using a Matrigel Implant in Mouse**

In vivo angiogenesis assay of a polypeptide of the invention measures the ability of an existing capillary network to form new vessels in an implanted capsule of murine extracellular matrix material (Matrigel). The protein is mixed with the liquid Matrigel at 4
25 degree C and the mixture is then injected subcutaneously in mice where it solidifies. After 7 days, the solid "plug" of Matrigel is removed and examined for the presence of new blood vessels. Matrigel is purchased from Becton Dickinson Labware/Collaborative Biomedical Products.

When thawed at 4 degree C the Matrigel material is a liquid. The Matrigel is
30 mixed with a polypeptide of the invention at 150 ng/ml at 4 degrees C and drawn into cold 3 ml syringes. Female C57Bl/6 mice approximately 8 weeks old are injected with the

mixture of Matrigel and experimental protein at 2 sites at the midventral aspect of the abdomen (0.5 ml/site). After 7 days, the mice are sacrificed by cervical dislocation, the Matrigel plugs are removed and cleaned (i.e., all clinging membranes and fibrous tissue is removed). Replicate whole plugs are fixed in neutral buffered 10% formaldehyde, embedded in paraffin and used to produce sections for histological examination after staining with Masson's Trichrome. Cross sections from 3 different regions of each plug are processed. Selected sections are stained for the presence of vWF. The positive control for this assay is bovine basic FGF (150 ng/ml). Matrigel alone is used to determine basal levels of angiogenesis.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

Example 44: Rescue of Ischemia in Rabbit Lower Limb Model

To study the in vivo effects of polynucleotides and polypeptides of the invention on ischemia, a rabbit hindlimb ischemia model is created by surgical removal of one femoral arteries as described previously (Takeshita *et al.*, *Am J. Pathol* 147:1649-1660 (1995)). The excision of the femoral artery results in retrograde propagation of thrombus and occlusion of the external iliac artery. Consequently, blood flow to the ischemic limb is dependent upon collateral vessels originating from the internal iliac artery (Takeshita *et al.* *Am J. Pathol* 147:1649-1660 (1995)). An interval of 10 days is allowed for post-operative recovery of rabbits and development of endogenous collateral vessels. At 10 day post-operatively (day 0), after performing a baseline angiogram, the internal iliac artery of the ischemic limb is transfected with 500 mg naked expression plasmid containing a polynucleotide of the invention by arterial gene transfer technology using a hydrogel-coated balloon catheter as described (Riessen *et al.* *Hum Gene Ther.* 4:749-758 (1993); Leclerc *et al.* *J. Clin. Invest.* 90: 936-944 (1992)). When a polypeptide of the invention is used in the treatment, a single bolus of 500 mg polypeptide of the invention or control is delivered into the internal iliac artery of the ischemic limb over a period of 1

min. through an infusion catheter. On day 30, various parameters are measured in these rabbits: (a) BP ratio - The blood pressure ratio of systolic pressure of the ischemic limb to that of normal limb; (b) Blood Flow and Flow Reserve - Resting FL: the blood flow during undilated condition and Max FL: the blood flow during fully dilated condition (also an indirect measure of the blood vessel amount) and Flow Reserve is reflected by the ratio of max FL: resting FL; (c) Angiographic Score - This is measured by the angiogram of collateral vessels. A score is determined by the percentage of circles in an overlaying grid that with crossing opacified arteries divided by the total number in the rabbit thigh; (d) Capillary density - The number of collateral capillaries determined in light microscopic sections taken from hindlimbs.

The studies described in this example tested activity of polynucleotides and polypeptides of the invention. However, one skilled in the art could easily modify the exemplified studies to test the agonists, and/or antagonists of the invention.

Example 45: Effect of Polypeptides of the Invention on Vasodilation

Since dilation of vascular endothelium is important in reducing blood pressure, the ability of polypeptides of the invention to affect the blood pressure in spontaneously hypertensive rats (SHR) is examined. Increasing doses (0, 10, 30, 100, 300, and 900 mg/kg) of the polypeptides of the invention are administered to 13-14 week old spontaneously hypertensive rats (SHR). Data are expressed as the mean +/- SEM. Statistical analysis are performed with a paired t-test and statistical significance is defined as $p < 0.05$ vs. the response to buffer alone.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

Example 46: Rat Ischemic Skin Flap Model

The evaluation parameters include skin blood flow, skin temperature, and factor VIII immunohistochemistry or endothelial alkaline phosphatase reaction. Expression of

polypeptides of the invention, during the skin ischemia, is studied using in situ hybridization.

The study in this model is divided into three parts as follows:

Ischemic skin

5 Ischemic skin wounds

Normal wounds

The experimental protocol includes:

Raising a 3x4 cm, single pedicle full-thickness random skin flap (myocutaneous flap over the lower back of the animal).

10 An excisional wounding (4-6 mm in diameter) in the ischemic skin (skin-flap).

Topical treatment with a polypeptide of the invention of the excisional wounds (day 0, 1, 2, 3, 4 post-wounding) at the following various dosage ranges: 1mg to 100 mg.

Harvesting the wound tissues at day 3, 5, 7, 10, 14 and 21 post-wounding for histological, immunohistochemical, and in situ studies.

15 The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

20 **Example 47: Peripheral Arterial Disease Model**

Angiogenic therapy using a polypeptide of the invention is a novel therapeutic strategy to obtain restoration of blood flow around the ischemia in case of peripheral arterial diseases. The experimental protocol includes:

25 One side of the femoral artery is ligated to create ischemic muscle of the hindlimb, the other side of hindlimb serves as a control.

A polypeptide of the invention, in a dosage range of 20 mg - 500 mg, is delivered intravenously and/or intramuscularly 3 times (perhaps more) per week for 2-3 weeks.

30 The ischemic muscle tissue is collected after ligation of the femoral artery at 1, 2, and 3 weeks for the analysis of expression of a polypeptide of the invention and histology. Biopsy is also performed on the other side of normal muscle of the contralateral hindlimb.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

5

Example 48: Ischemic Myocardial Disease Model

A polypeptide of the invention is evaluated as a potent mitogen capable of stimulating the development of collateral vessels, and restructuring new vessels after coronary artery occlusion. Alteration of expression of the polypeptide is investigated in situ. The experimental protocol includes:

The heart is exposed through a left-side thoracotomy in the rat. Immediately, the left coronary artery is occluded with a thin suture (6-0) and the thorax is closed.

A polypeptide of the invention, in a dosage range of 20 mg - 500 mg, is delivered intravenously and/or intramuscularly 3 times (perhaps more) per week for 2-4 weeks.

Thirty days after the surgery, the heart is removed and cross-sectioned for morphometric and in situ analyzes.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

Example 49: Rat Corneal Wound Healing Model

This animal model shows the effect of a polypeptide of the invention on neovascularization. The experimental protocol includes:

Making a 1-1.5 mm long incision from the center of cornea into the stromal layer. Inserting a spatula below the lip of the incision facing the outer corner of the eye. Making a pocket (its base is 1-1.5 mm from the edge of the eye). Positioning a pellet, containing 50ng- 5ug of a polypeptide of the invention, within the pocket.

Treatment with a polypeptide of the invention can also be applied topically to the corneal wounds in a dosage range of 20mg - 500mg (daily treatment for five days).

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

5

Example 50: Diabetic Mouse and Glucocorticoid-Impaired Wound Healing Models

Diabetic db+/db+ Mouse Model.

10 To demonstrate that a polypeptide of the invention accelerates the healing process, the genetically diabetic mouse model of wound healing is used. The full thickness wound healing model in the db+/db+ mouse is a well characterized, clinically relevant and reproducible model of impaired wound healing. Healing of the diabetic wound is dependent on formation of granulation tissue and re-epithelialization rather than
15 contraction (Gartner, M.H. *et al.*, *J. Surg. Res.* 52:389 (1992); Greenhalgh, D.G. *et al.*, *Am. J. Pathol.* 136:1235 (1990)).

The diabetic animals have many of the characteristic features observed in Type II diabetes mellitus. Homozygous (db+/db+) mice are obese in comparison to their normal heterozygous (db+/+m) littermates. Mutant diabetic (db+/db+) mice have a single
20 autosomal recessive mutation on chromosome 4 (db+) (Coleman *et al.* *Proc. Natl. Acad. Sci. USA* 77:283-293 (1982)). Animals show polyphagia, polydipsia and polyuria. Mutant diabetic mice (db+/db+) have elevated blood glucose, increased or normal insulin levels, and suppressed cell-mediated immunity (Mandel *et al.*, *J. Immunol.* 120:1375 (1978); Debray-Sachs, M. *et al.*, *Clin. Exp. Immunol.* 51(1):1-7 (1983); Leiter *et al.*, *Am.*
25 *J. of Pathol.* 114:46-55 (1985)). Peripheral neuropathy, myocardial complications, and microvascular lesions, basement membrane thickening and glomerular filtration abnormalities have been described in these animals (Norido, F. *et al.*, *Exp. Neurol.* 83(2):221-232 (1984); Robertson *et al.*, *Diabetes* 29(1):60-67 (1980); Giacomelli *et al.*, *Lab Invest.* 40(4):460-473 (1979); Coleman, D.L., *Diabetes* 31 (Suppl):1-6 (1982)). These
30 homozygous diabetic mice develop hyperglycemia that is resistant to insulin analogous to human type II diabetes (Mandel *et al.*, *J. Immunol.* 120:1375-1377 (1978)).

The characteristics observed in these animals suggests that healing in this model may be similar to the healing observed in human diabetes (Greenhalgh, *et al.*, *Am. J. of Pathol.* 136:1235-1246 (1990)).

Genetically diabetic female C57BL/KsJ (db+/db+) mice and their non-diabetic
5 (db+/+m) heterozygous littermates are used in this study (Jackson Laboratories). The animals are purchased at 6 weeks of age and are 8 weeks old at the beginning of the study. Animals are individually housed and received food and water ad libitum. All manipulations are performed using aseptic techniques. The experiments are conducted according to the rules and guidelines of Human Genome Sciences, Inc. Institutional
10 Animal Care and Use Committee and the Guidelines for the Care and Use of Laboratory Animals.

Wounding protocol is performed according to previously reported methods (Tsuboi, R. and Rifkin, D.B., *J. Exp. Med.* 172:245-251 (1990)). Briefly, on the day of wounding, animals are anesthetized with an intraperitoneal injection of Avertin (0.01
15 mg/mL), 2,2,2-tribromoethanol and 2-methyl-2-butanol dissolved in deionized water. The dorsal region of the animal is shaved and the skin washed with 70% ethanol solution and iodine. The surgical area is dried with sterile gauze prior to wounding. An 8 mm full-thickness wound is then created using a Keyes tissue punch. Immediately following wounding, the surrounding skin is gently stretched to eliminate wound expansion. The
20 wounds are left open for the duration of the experiment. Application of the treatment is given topically for 5 consecutive days commencing on the day of wounding. Prior to treatment, wounds are gently cleansed with sterile saline and gauze sponges.

Wounds are visually examined and photographed at a fixed distance at the day of surgery and at two day intervals thereafter. Wound closure is determined by daily
25 measurement on days 1-5 and on day 8. Wounds are measured horizontally and vertically using a calibrated Jameson caliper. Wounds are considered healed if granulation tissue is no longer visible and the wound is covered by a continuous epithelium.

A polypeptide of the invention is administered using at a range different doses, from 4mg to 500mg per wound per day for 8 days in vehicle. Vehicle control groups
30 received 50mL of vehicle solution.

Animals are euthanized on day 8 with an intraperitoneal injection of sodium pentobarbital (300mg/kg). The wounds and surrounding skin are then harvested for

histology and immunohistochemistry. Tissue specimens are placed in 10% neutral buffered formalin in tissue cassettes between biopsy sponges for further processing.

Three groups of 10 animals each (5 diabetic and 5 non-diabetic controls) are evaluated: 1) Vehicle placebo control, 2) untreated group, and 3) treated group.

5 Wound closure is analyzed by measuring the area in the vertical and horizontal axis and obtaining the total square area of the wound. Contraction is then estimated by establishing the differences between the initial wound area (day 0) and that of post treatment (day 8). The wound area on day 1 is 64mm², the corresponding size of the dermal punch. Calculations are made using the following formula:

10

$$[\text{Open area on day 8}] - [\text{Open area on day 1}] / [\text{Open area on day 1}]$$

Specimens are fixed in 10% buffered formalin and paraffin embedded blocks are sectioned perpendicular to the wound surface (5mm) and cut using a Reichert-Jung
15 microtome. Routine hematoxylin-eosin (H&E) staining is performed on cross-sections of bisected wounds. Histologic examination of the wounds are used to assess whether the healing process and the morphologic appearance of the repaired skin is altered by treatment with a polypeptide of the invention. This assessment included verification of the presence of cell accumulation, inflammatory cells, capillaries, fibroblasts, re-
20 epithelialization and epidermal maturity (Greenhalgh, D.G. *et al.*, *Am. J. Pathol.* 136:1235 (1990)). A calibrated lens micrometer is used by a blinded observer.

Tissue sections are also stained immunohistochemically with a polyclonal rabbit anti-human keratin antibody using ABC Elite detection system. Human skin is used as a positive tissue control while non-immune IgG is used as a negative control. Keratinocyte
25 growth is determined by evaluating the extent of reepithelialization of the wound using a calibrated lens micrometer.

Proliferating cell nuclear antigen/cyclin (PCNA) in skin specimens is demonstrated by using anti-PCNA antibody (1:50) with an ABC Elite detection system. Human colon cancer can serve as a positive tissue control and human brain tissue can be used as a
30 negative tissue control. Each specimen includes a section with omission of the primary antibody and substitution with non-immune mouse IgG. Ranking of these sections is

based on the extent of proliferation on a scale of 0-8, the lower side of the scale reflecting slight proliferation to the higher side reflecting intense proliferation.

Experimental data are analyzed using an unpaired t test. A p value of < 0.05 is considered significant.

5

Steroid Impaired Rat Model

The inhibition of wound healing by steroids has been well documented in various *in vitro* and *in vivo* systems (Wahl, Glucocorticoids and Wound healing. In: Anti-Inflammatory Steroid Action: Basic and Clinical Aspects. 280-302 (1989); Wahl *et al.*, *J. Immunol.* 115: 476-481 (1975); Werb *et al.*, *J. Exp. Med.* 147:1684-1694 (1978)).

10

Glucocorticoids retard wound healing by inhibiting angiogenesis, decreasing vascular permeability (Ebert *et al.*, *Am. Intern. Med.* 37:701-705 (1952)), fibroblast proliferation, and collagen synthesis (Beck *et al.*, *Growth Factors.* 5: 295-304 (1991); Haynes *et al.*, *J. Clin. Invest.* 61: 703-797 (1978)) and producing a transient reduction of circulating monocytes (Haynes *et al.*, *J. Clin. Invest.* 61: 703-797 (1978); Wahl, "Glucocorticoids and wound healing", In: Antiinflammatory Steroid Action: Basic and Clinical Aspects, Academic Press, New York, pp. 280-302 (1989)). The systemic administration of steroids to impaired wound healing is a well establish phenomenon in rats (Beck *et al.*, *Growth Factors.* 5: 295-304 (1991); Haynes *et al.*, *J. Clin. Invest.* 61: 703-797 (1978); Wahl, "Glucocorticoids and wound healing", In: Antiinflammatory Steroid Action: Basic and Clinical Aspects, Academic Press, New York, pp. 280-302 (1989); Pierce *et al.*, *Proc. Natl. Acad. Sci. USA* 86: 2229-2233 (1989)).

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To demonstrate that a polypeptide of the invention can accelerate the healing process, the effects of multiple topical applications of the polypeptide on full thickness excisional skin wounds in rats in which healing has been impaired by the systemic administration of methylprednisolone is assessed.

Young adult male Sprague Dawley rats weighing 250-300 g (Charles River Laboratories) are used in this example. The animals are purchased at 8 weeks of age and are 9 weeks old at the beginning of the study. The healing response of rats is impaired by the systemic administration of methylprednisolone (17mg/kg/rat intramuscularly) at the time of wounding. Animals are individually housed and received food and water *ad libitum*. All manipulations are performed using aseptic techniques. This study is

30

conducted according to the rules and guidelines of Human Genome Sciences, Inc. Institutional Animal Care and Use Committee and the Guidelines for the Care and Use of Laboratory Animals.

The wounding protocol is followed according to section A, above. On the day of
5 wounding, animals are anesthetized with an intramuscular injection of ketamine (50 mg/kg) and xylazine (5 mg/kg). The dorsal region of the animal is shaved and the skin washed with 70% ethanol and iodine solutions. The surgical area is dried with sterile gauze prior to wounding. An 8 mm full-thickness wound is created using a Keyes tissue punch. The wounds are left open for the duration of the experiment. Applications of the
10 testing materials are given topically once a day for 7 consecutive days commencing on the day of wounding and subsequent to methylprednisolone administration. Prior to treatment, wounds are gently cleansed with sterile saline and gauze sponges.

Wounds are visually examined and photographed at a fixed distance at the day of wounding and at the end of treatment. Wound closure is determined by daily measurement
15 on days 1-5 and on day 8. Wounds are measured horizontally and vertically using a calibrated Jameson caliper. Wounds are considered healed if granulation tissue is no longer visible and the wound is covered by a continuous epithelium.

The polypeptide of the invention is administered using at a range different doses, from 4mg to 500mg per wound per day for 8 days in vehicle. Vehicle control groups
20 received 50mL of vehicle solution.

Animals are euthanized on day 8 with an intraperitoneal injection of sodium pentobarbital (300mg/kg). The wounds and surrounding skin are then harvested for histology. Tissue specimens are placed in 10% neutral buffered formalin in tissue cassettes between biopsy sponges for further processing.

25 Four groups of 10 animals each (5 with methylprednisolone and 5 without glucocorticoid) are evaluated: 1) Untreated group 2) Vehicle placebo control 3) treated groups.

Wound closure is analyzed by measuring the area in the vertical and horizontal axis and obtaining the total area of the wound. Closure is then estimated by establishing
30 the differences between the initial wound area (day 0) and that of post treatment (day 8). The wound area on day 1 is 64mm², the corresponding size of the dermal punch. Calculations are made using the following formula:

[Open area on day 8] - [Open area on day 1] / [Open area on day 1]

Specimens are fixed in 10% buffered formalin and paraffin embedded blocks are
5 sectioned perpendicular to the wound surface (5mm) and cut using an Olympus
microtome. Routine hematoxylin-eosin (H&E) staining is performed on cross-sections of
bisected wounds. Histologic examination of the wounds allows assessment of whether the
healing process and the morphologic appearance of the repaired skin is improved by
treatment with a polypeptide of the invention. A calibrated lens micrometer is used by a
10 blinded observer to determine the distance of the wound gap.

Experimental data are analyzed using an unpaired t test. A p value of < 0.05 is
considered significant.

The studies described in this example tested activity of a polypeptide of the
invention. However, one skilled in the art could easily modify the exemplified studies to
15 test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the
invention.

Example 51: Lymphadema Animal Model

20 The purpose of this experimental approach is to create an appropriate and
consistent lymphedema model for testing the therapeutic effects of a polypeptide of the
invention in lymphangiogenesis and re-establishment of the lymphatic circulatory system
in the rat hind limb. Effectiveness is measured by swelling volume of the affected limb,
quantification of the amount of lymphatic vasculature, total blood plasma protein, and
25 histopathology. Acute lymphedema is observed for 7-10 days. Perhaps more importantly,
the chronic progress of the edema is followed for up to 3-4 weeks.

Prior to beginning surgery, blood sample is drawn for protein concentration
analysis. Male rats weighing approximately ~350g are dosed with Pentobarbital.
Subsequently, the right legs are shaved from knee to hip. The shaved area is swabbed
30 with gauze soaked in 70% EtOH. Blood is drawn for serum total protein testing.
Circumference and volumetric measurements are made prior to injecting dye into paws
after marking 2 measurement levels (0.5 cm above heel, at mid-pt of dorsal paw). The

intradermal dorsum of both right and left paws are injected with 0.05 ml of 1% Evan's Blue. Circumference and volumetric measurements are then made following injection of dye into paws.

- Using the knee joint as a landmark, a mid-leg inguinal incision is made
- 5 circumferentially allowing the femoral vessels to be located. Forceps and hemostats are used to dissect and separate the skin flaps. After locating the femoral vessels, the lymphatic vessel that runs along side and underneath the vessel(s) is located. The main lymphatic vessels in this area are then electrically coagulated suture ligated.

- Using a microscope, muscles in back of the leg (near the semitendinosus and
- 10 adductors) are bluntly dissected. The popliteal lymph node is then located. The 2 proximal and 2 distal lymphatic vessels and distal blood supply of the popliteal node are then and ligated by suturing. The popliteal lymph node, and any accompanying adipose tissue, is then removed by cutting connective tissues.

- Care is taken to control any mild bleeding resulting from this procedure. After
- 15 lymphatics are occluded, the skin flaps are sealed by using liquid skin (Vetbond) (AJ Buck). The separated skin edges are sealed to the underlying muscle tissue while leaving a gap of ~0.5 cm around the leg. Skin also may be anchored by suturing to underlying muscle when necessary.

- To avoid infection, animals are housed individually with mesh (no bedding).
- 20 Recovering animals are checked daily through the optimal edematous peak, which typically occurred by day 5-7. The plateau edematous peak are then observed. To evaluate the intensity of the lymphedema, the circumference and volumes of 2 designated places on each paw before operation and daily for 7 days are measured. The effect plasma proteins on lymphedema is determined and whether protein analysis is a useful testing
- 25 perimeter is also investigated. The weights of both control and edematous limbs are evaluated at 2 places. Analysis is performed in a blind manner.

- Circumference Measurements: Under brief gas anesthetic to prevent limb movement, a cloth tape is used to measure limb circumference. Measurements are done at the ankle bone and dorsal paw by 2 different people then those 2 readings are averaged.
- 30 Readings are taken from both control and edematous limbs.

Volumetric Measurements: On the day of surgery, animals are anesthetized with Pentobarbital and are tested prior to surgery. For daily volumetrics animals are under

brief halothane anesthetic (rapid immobilization and quick recovery), both legs are shaved and equally marked using waterproof marker on legs. Legs are first dipped in water, then dipped into instrument to each marked level then measured by Buxco edema software(Chen/Victor). Data is recorded by one person, while the other is dipping the limb to marked area.

Blood-plasma protein measurements: Blood is drawn, spun, and serum separated prior to surgery and then at conclusion for total protein and Ca^{2+} comparison.

Limb Weight Comparison: After drawing blood, the animal is prepared for tissue collection. The limbs are amputated using a quillitine, then both experimental and control legs are cut at the ligature and weighed. A second weighing is done as the tibio-cacaneal joint is disarticulated and the foot is weighed.

Histological Preparations: The transverse muscle located behind the knee (popliteal) area is dissected and arranged in a metal mold, filled with freezeGel, dipped into cold methylbutane, placed into labeled sample bags at -80°C until sectioning. Upon sectioning, the muscle is observed under fluorescent microscopy for lymphatics..

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

Example 52: Suppression of TNF alpha-induced adhesion molecule expression by a Polypeptide of the Invention

The recruitment of lymphocytes to areas of inflammation and angiogenesis involves specific receptor-ligand interactions between cell surface adhesion molecules (CAMs) on lymphocytes and the vascular endothelium. The adhesion process, in both normal and pathological settings, follows a multi-step cascade that involves intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and endothelial leukocyte adhesion molecule-1 (E-selectin) expression on endothelial cells (EC). The expression of these molecules and others on the vascular endothelium determines the efficiency with which leukocytes may adhere to the local vasculature and extravasate into the local tissue during the development of an inflammatory response. The

local concentration of cytokines and growth factor participate in the modulation of the expression of these CAMs.

Tumor necrosis factor alpha (TNF- α), a potent proinflammatory cytokine, is a stimulator of all three CAMs on endothelial cells and may be involved in a wide variety of inflammatory responses, often resulting in a pathological outcome.

The potential of a polypeptide of the invention to mediate a suppression of TNF- α induced CAM expression can be examined. A modified ELISA assay which uses ECs as a solid phase absorbent is employed to measure the amount of CAM expression on TNF- α treated ECs when co-stimulated with a member of the FGF family of proteins.

To perform the experiment, human umbilical vein endothelial cell (HUVEC) cultures are obtained from pooled cord harvests and maintained in growth medium (EGM-2; Clonetics, San Diego, CA) supplemented with 10% FCS and 1% penicillin/streptomycin in a 37 degree C humidified incubator containing 5% CO₂.

HUVECs are seeded in 96-well plates at concentrations of 1×10^4 cells/well in EGM medium at 37 degree C for 18-24 hrs or until confluent. The monolayers are subsequently washed 3 times with a serum-free solution of RPMI-1640 supplemented with 100 U/ml penicillin and 100 mg/ml streptomycin, and treated with a given cytokine and/or growth factor(s) for 24 h at 37 degree C. Following incubation, the cells are then evaluated for CAM expression.

Human Umbilical Vein Endothelial cells (HUVECs) are grown in a standard 96 well plate to confluence. Growth medium is removed from the cells and replaced with 90 μ l of 199 Medium (10% FBS). Samples for testing and positive or negative controls are added to the plate in triplicate (in 10 μ l volumes). Plates are incubated at 37 degree C for either 5 h (selectin and integrin expression) or 24 h (integrin expression only). Plates are aspirated to remove medium and 100 μ l of 0.1% paraformaldehyde-PBS(with Ca⁺⁺ and Mg⁺⁺) is added to each well. Plates are held at 4°C for 30 min.

Fixative is then removed from the wells and wells are washed 1X with PBS(+Ca,Mg)+0.5% BSA and drained. Do not allow the wells to dry. Add 10 μ l of diluted primary antibody to the test and control wells. Anti-ICAM-1-Biotin, Anti-VCAM-1-Biotin and Anti-E-selectin-Biotin are used at a concentration of 10 μ g/ml (1:10 dilution of 0.1 mg/ml stock antibody). Cells are incubated at 37°C for 30 min. in a humidified environment. Wells are washed X3 with PBS(+Ca,Mg)+0.5% BSA.

Then add 20 μ l of diluted ExtrAvidin-Alkaline Phosphatase (1:5,000 dilution) to each well and incubated at 37°C for 30 min. Wells are washed X3 with PBS(+Ca,Mg)+0.5% BSA. 1 tablet of p-Nitrophenol Phosphate pNPP is dissolved in 5 ml of glycine buffer (pH 10.4). 100 μ l of pNPP substrate in glycine buffer is added to each test well. Standard wells in triplicate are prepared from the working dilution of the ExtrAvidin-Alkaline Phosphatase in glycine buffer: 1:5,000 (10^0) > $10^{-0.5}$ > 10^{-1} > $10^{-1.5}$. 5 μ l of each dilution is added to triplicate wells and the resulting AP content in each well is 5.50 ng, 1.74 ng, 0.55 ng, 0.18 ng. 100 μ l of pNPP reagent must then be added to each of the standard wells. The plate must be incubated at 37°C for 4h. A volume of 50 μ l of 3M NaOH is added to all wells. The results are quantified on a plate reader at 405 nm. The background subtraction option is used on blank wells filled with glycine buffer only. The template is set up to indicate the concentration of AP-conjugate in each standard well [5.50 ng; 1.74 ng; 0.55 ng; 0.18 ng]. Results are indicated as amount of bound AP-conjugate in each sample.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

Example 53: Assay for the Stimulation of Bone Marrow CD34+ Cell Proliferation

This assay is based on the ability of human CD34+ to proliferate in the presence of hematopoietic growth factors and evaluates the ability of isolated polypeptides expressed in mammalian cells to stimulate proliferation of CD34+ cells.

It has been previously shown that most mature precursors will respond to only a single signal. More immature precursors require at least two signals to respond. Therefore, to test the effect of polypeptides on hematopoietic activity of a wide range of progenitor cells, the assay contains a given polypeptide in the presence or absence of other hematopoietic growth factors. Isolated cells are cultured for 5 days in the presence of Stem Cell Factor (SCF) in combination with tested sample. SCF alone has a very limited effect on the proliferation of bone marrow (BM) cells, acting in such conditions only as a "survival" factor. However, combined with any factor

exhibiting stimulatory effect on these cells (e.g., IL-3), SCF will cause a synergistic effect. Therefore, if the tested polypeptide has a stimulatory effect on a hematopoietic progenitors, such activity can be easily detected. Since normal BM cells have a low level of cycling cells, it is likely that any inhibitory effect of a given polypeptide, or
5 agonists or antagonists thereof, might not be detected. Accordingly, assays for an inhibitory effect on progenitors is preferably tested in cells that are first subjected to *in vitro* stimulation with SCF+IL-3, and then contacted with the compound that is being evaluated for inhibition of such induced proliferation.

Briefly, CD34+ cells are isolated using methods known in the art. The cells
10 are thawed and resuspended in medium (QBSF 60 serum-free medium with 1% L-glutamine (500ml) Quality Biological, Inc., Gaithersburg, MD Cat# 160-204-101). After several gentle centrifugation steps at 200 x g, cells are allowed to rest for one hour. The cell count is adjusted to 2.5×10^5 cells/ml. During this time, 100 μ l of sterile water is added to the peripheral wells of a 96-well plate. The cytokines that
15 can be tested with a given polypeptide in this assay is rhSCF (R&D Systems, Minneapolis, MN, Cat# 255-SC) at 50 ng/ml alone and in combination with rhSCF and rhIL-3 (R&D Systems, Minneapolis, MN, Cat# 203-ML) at 30 ng/ml. After one hour, 10 μ l of prepared cytokines, 50 μ l SID (supernatants at 1:2 dilution = 50 μ l) and 20 μ l of diluted cells are added to the media which is already present in the wells to
20 allow for a final total volume of 100 μ l. The plates are then placed in a 37°C/5% CO₂ incubator for five days.

Eighteen hours before the assay is harvested, 0.5 μ Ci/well of [3H] Thymidine is added in a 10 μ l volume to each well to determine the proliferation rate. The experiment is terminated by harvesting the cells from each 96-well plate to a filtermat
25 using the Tomtec Harvester 96. After harvesting, the filtermats are dried, trimmed and placed into OmniFilter assemblies consisting of one OmniFilter plate and one OmniFilter Tray. 60 μ l Microscint is added to each well and the plate sealed with TopSeal-A press-on sealing film. A bar code 15 sticker is affixed to the first plate for counting. The sealed plates is then loaded and the level of radioactivity determined
30 via the Packard Top Count and the printed data collected for analysis. The level of radioactivity reflects the amount of cell proliferation.

The studies described in this example test the activity of a given polypeptide to stimulate bone marrow CD34+ cell proliferation. One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof.

5 As a nonlimiting example, potential antagonists tested in this assay would be expected to inhibit cell proliferation in the presence of cytokines and/or to increase the inhibition of cell proliferation in the presence of cytokines and a given polypeptide. In contrast, potential agonists tested in this assay would be expected to enhance cell proliferation and/or to decrease the inhibition of cell proliferation in the presence of
10 cytokines and a given polypeptide.

The ability of a gene to stimulate the proliferation of bone marrow CD34+ cells indicates that polynucleotides and polypeptides corresponding to the gene are useful for the diagnosis and treatment of disorders affecting the immune system and hematopoiesis. Representative uses are described in the “Immune Activity” and
15 “Infectious Disease” sections above, and elsewhere herein.

Example 54: Assay for Extracellular Matrix Enhanced Cell Response (EMECCR)

The objective of the Extracellular Matrix Enhanced Cell Response (EMECCR) assay is to identify gene products (e.g., isolated polypeptides) that act on the
20 hematopoietic stem cells in the context of the extracellular matrix (ECM) induced signal.

Cells respond to the regulatory factors in the context of signal(s) received from the surrounding microenvironment. For example, fibroblasts, and endothelial and epithelial stem cells fail to replicate in the absence of signals from the ECM.
25 Hematopoietic stem cells can undergo self-renewal in the bone marrow, but not in *in vitro* suspension culture. The ability of stem cells to undergo self-renewal *in vitro* is dependent upon their interaction with the stromal cells and the ECM protein fibronectin (fn). Adhesion of cells to fn is mediated by the $\alpha_5\beta_1$ and $\alpha_4\beta_1$ integrin receptors, which are expressed by human and mouse hematopoietic stem cells. The
30 factor(s) which integrate with the ECM environment and responsible for stimulating stem cell self-renewal has not yet been identified. Discovery of such factors should be of great interest in gene therapy and bone marrow transplant applications

Briefly, polystyrene, non tissue culture treated, 96-well plates are coated with fn fragment at a coating concentration of $0.2 \mu\text{g}/\text{cm}^2$. Mouse bone marrow cells are plated (1,000 cells/well) in 0.2 ml of serum-free medium. Cells cultured in the presence of IL-3 (5 ng/ml) + SCF (50 ng/ml) would serve as the positive control, conditions under which little self-renewal but pronounced differentiation of the stem cells is to be expected. Gene products are tested with appropriate negative controls in the presence and absence of SCF(5.0 ng/ml), where test factor supernates represent 10% of the total assay volume. The plated cells are then allowed to grow by incubating in a low oxygen environment (5% CO_2 , 7% O_2 , and 88% N_2) tissue culture incubator for 7 days. The number of proliferating cells within the wells is then quantitated by measuring thymidine incorporation into cellular DNA. Verification of the positive hits in the assay will require phenotypic characterization of the cells, which can be accomplished by scaling up of the culture system and using appropriate antibody reagents against cell surface antigens and FACScan.

One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof.

If a particular gene product is found to be a stimulator of hematopoietic progenitors, polynucleotides and polypeptides corresponding to the gene may be useful for the diagnosis and treatment of disorders affecting the immune system and hematopoiesis. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections above, and elsewhere herein. The gene product may also be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Additionally, the polynucleotides and/or polypeptides of the gene of interest and/or agonists and/or antagonists thereof, may also be employed to inhibit the proliferation and differentiation of hematopoietic cells and therefore may be employed to protect bone marrow stem cells from chemotherapeutic agents during chemotherapy. This antiproliferative effect may allow administration of higher doses of chemotherapeutic agents and, therefore, more effective chemotherapeutic treatment.

Moreover, polynucleotides and polypeptides corresponding to the gene of interest may also be useful for the treatment and diagnosis of hematopoietic related disorders such as, for example, anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia.

Example 55: Human Dermal Fibroblast and Aortic Smooth Muscle Cell

Proliferation

The polypeptide of interest is added to cultures of normal human dermal fibroblasts (NHDF) and human aortic smooth muscle cells (AoSMC) and two co-assays are performed with each sample. The first assay examines the effect of the polypeptide of interest on the proliferation of normal human dermal fibroblasts (NHDF) or aortic smooth muscle cells (AoSMC). Aberrant growth of fibroblasts or smooth muscle cells is a part of several pathological processes, including fibrosis, and restenosis. The second assay examines IL6 production by both NHDF and SMC. IL6 production is an indication of functional activation. Activated cells will have increased production of a number of cytokines and other factors, which can result in a proinflammatory or immunomodulatory outcome. Assays are run with and without co-TNF α stimulation, in order to check for costimulatory or inhibitory activity.

Briefly, on day 1, 96-well black plates are set up with 1000 cells/well (NHDF) or 2000 cells/well (AoSMC) in 100 μ l culture media. NHDF culture media contains: Clonetics FB basal media, 1mg/ml hFGF, 5mg/ml insulin, 50mg/ml gentamycin, 2%FBS, while AoSMC culture media contains Clonetics SM basal media, 0.5 μ g/ml hEGF, 5mg/ml insulin, 1 μ g/ml hFGF, 50mg/ml gentamycin, 50 μ g/ml Amphotericin B, 5%FBS. After incubation @ 37°C for at least 4-5 hours culture media is aspirated and replaced with growth arrest media. Growth arrest media for NHDF contains fibroblast basal media, 50mg/ml gentamycin, 2% FBS, while growth arrest media for AoSMC contains SM basal media, 50mg/ml gentamycin, 50 μ g/ml Amphotericin B, 0.4% FBS. Incubate at 37C until day 2.

On day 2, serial dilutions and templates of the polypeptide of interest are designed which should always include media controls and known-protein controls. For both stimulation and inhibition experiments, proteins are diluted in growth arrest media. For inhibition experiments, TNF α is added to a final concentration of 2ng/ml (NHDF) or 5ng/ml (AoSMC). Then add 1/3 vol media containing controls or supernatants and incubate at 37C/5% CO₂ until day 5.

Transfer 60 μ l from each well to another labeled 96-well plate, cover with a plate-sealer, and store at 4C until Day 6 (for IL6 ELISA). To the remaining 100 μ l in the cell culture plate, aseptically add Alamar Blue in an amount equal to 10% of the culture volume (10 μ l). Return plates to incubator for 3 to 4 hours. Then measure fluorescence with excitation at 530nm and emission at 590nm using the CytoFluor. This yields the growth stimulation/inhibition data.

On day 5, the IL6 ELISA is performed by coating a 96 well plate with 50-100 μ l/well of Anti-Human IL6 Monoclonal antibody diluted in PBS, pH 7.4, incubate ON at room temperature.

On day 6, empty the plates into the sink and blot on paper towels. Prepare Assay Buffer containing PBS with 4% BSA. Block the plates with 200 μ l/well of Pierce Super Block blocking buffer in PBS for 1-2 hr and then wash plates with wash buffer (PBS, 0.05% Tween-20). Blot plates on paper towels. Then add 50 μ l/well of diluted Anti-Human IL-6 Monoclonal, Biotin-labeled antibody at 0.50 mg/ml. Make dilutions of IL-6 stock in media (30, 10, 3, 1, 0.3, 0 ng/ml). Add duplicate samples to top row of plate. Cover the plates and incubate for 2 hours at RT on shaker.

Wash plates with wash buffer and blot on paper towels. Dilute EU-labeled Streptavidin 1:1000 in Assay buffer, and add 100 μ l/well. Cover the plate and incubate 1 h at RT. Wash plates with wash buffer. Blot on paper towels.

Add 100 μ l/well of Enhancement Solution. Shake for 5 minutes. Read the plate on the Wallac DELFIA Fluorometer. Readings from triplicate samples in each assay were tabulated and averaged.

A positive result in this assay suggests AoSMC cell proliferation and that the gene product of interest may be involved in dermal fibroblast proliferation and/or smooth muscle cell proliferation. A positive result also suggests many potential uses of polypeptides, polynucleotides, agonists and/or antagonists of the gene/gene product

of interest. For example, inflammation and immune responses, wound healing, and angiogenesis, as detailed throughout this specification. Particularly, polypeptides of the gene product and polynucleotides of the gene may be used in wound healing and dermal regeneration, as well as the promotion of vasculargenesis, both of the blood vessels and lymphatics. The growth of vessels can be used in the treatment of, for example, cardiovascular diseases. Additionally, antagonists of polypeptides of the gene product and polynucleotides of the gene may be useful in treating diseases, disorders, and/or conditions which involve angiogenesis by acting as an anti-vascular (e.g., anti-angiogenesis). These diseases, disorders, and/or conditions are known in the art and/or are described herein, such as, for example, malignancies, solid tumors, benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas; arteriosclerotic plaques; ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, uveitis and Pterygia (abnormal blood vessel growth) of the eye; rheumatoid arthritis; psoriasis; delayed wound healing; endometriosis; vasculogenesis; granulations; hypertrophic scars (keloids); nonunion fractures; scleroderma; trachoma; vascular adhesions; myocardial angiogenesis; coronary collaterals; cerebral collaterals; arteriovenous malformations; ischemic limb angiogenesis; Osler-Webber Syndrome; plaque neovascularization; telangiectasia; hemophilic joints; angiofibroma; fibromuscular dysplasia; wound granulation; Crohn's disease; and atherosclerosis. Moreover, antagonists of polypeptides of the gene product and polynucleotides of the gene may be useful in treating anti-hyperproliferative diseases and/or anti-inflammatory known in the art and/or described herein.

One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof.

Example 56: Cellular Adhesion Molecule (CAM) Expression on Endothelial Cells

The recruitment of lymphocytes to areas of inflammation and angiogenesis involves specific receptor-ligand interactions between cell surface adhesion molecules (CAMs) on lymphocytes and the vascular endothelium. The adhesion process, in both normal and pathological settings, follows a multi-step cascade that involves intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and endothelial leukocyte adhesion molecule-1 (E-selectin) expression on endothelial cells (EC). The expression of these molecules and others on the vascular endothelium determines the efficiency with which leukocytes may adhere to the local vasculature and extravasate into the local tissue during the development of an inflammatory response. The local concentration of cytokines and growth factor participate in the modulation of the expression of these CAMs.

Briefly, endothelial cells (e.g., Human Umbilical Vein Endothelial cells (HUVECs)) are grown in a standard 96 well plate to confluence, growth medium is removed from the cells and replaced with 100 μ l of 199 Medium (10% fetal bovine serum (FBS)). Samples for testing and positive or negative controls are added to the plate in triplicate (in 10 μ l volumes). Plates are then incubated at 37°C for either 5 h (selectin and integrin expression) or 24 h (integrin expression only). Plates are aspirated to remove medium and 100 μ l of 0.1% paraformaldehyde-PBS(with Ca++ and Mg++) is added to each well. Plates are held at 4°C for 30 min. Fixative is removed from the wells and wells are washed 1X with PBS(+Ca,Mg) + 0.5% BSA and drained. 10 μ l of diluted primary antibody is added to the test and control wells. Anti-ICAM-1-Biotin, Anti-VCAM-1-Biotin and Anti-E-selectin-Biotin are used at a concentration of 10 μ g/ml (1:10 dilution of 0.1 mg/ml stock antibody). Cells are incubated at 37°C for 30 min. in a humidified environment. Wells are washed three times with PBS(+Ca,Mg) + 0.5% BSA. 20 μ l of diluted ExtrAvidin-Alkaline Phosphatase (1:5,000 dilution, referred to herein as the working dilution) are added to each well and incubated at 37°C for 30 min. Wells are washed three times with PBS(+Ca,Mg)+0.5% BSA. Dissolve 1 tablet of p-Nitrophenol Phosphate pNPP per 5 ml of glycine buffer (pH 10.4). 100 μ l of pNPP substrate in glycine buffer is added to each test well. Standard wells in triplicate are prepared from the working dilution of the ExtrAvidin-Alkaline Phosphatase in glycine buffer: 1:5,000 (10^0) > $10^{-0.5}$ > 10^{-1} > $10^{-1.5}$. 5 μ l of each dilution is added to triplicate wells and the resulting AP content in

each well is 5.50 ng, 1.74 ng, 0.55 ng, 0.18 ng. 100 μ l of pNNP reagent is then added to each of the standard wells. The plate is incubated at 37°C for 4h. A volume of 50 μ l of 3M NaOH is added to all wells. The plate is read on a plate reader at 405 nm using the background subtraction option on blank wells filled with glycine buffer only. Additionally, the template is set up to indicate the concentration of AP-conjugate in each standard well [5.50 ng; 1.74 ng; 0.55 ng; 0.18 ng]. Results are indicated as amount of bound AP-conjugate in each sample.

Example 57: Alamar Blue Endothelial Cells Proliferation Assay

10 This assay may be used to quantitatively determine protein mediated inhibition of bFGF-induced proliferation of Bovine Lymphatic Endothelial Cells (LECs), Bovine Aortic Endothelial Cells (BAECs) or Human Microvascular Uterine Myometrial Cells (UTMECs). This assay incorporates a fluorometric growth indicator based on detection of metabolic activity. A standard Alamar Blue
15 Proliferation Assay is prepared in EGM-2MV with 10 ng/ml of bFGF added as a source of endothelial cell stimulation. This assay may be used with a variety of endothelial cells with slight changes in growth medium and cell concentration. Dilutions of the protein batches to be tested are diluted as appropriate. Serum-free medium (GIBCO SFM) without bFGF is used as a non-stimulated control and
20 Angiostatin or TSP-1 are included as a known inhibitory controls.

Briefly, LEC, BAECs or UTMECs are seeded in growth media at a density of 5000 to 2000 cells/well in a 96 well plate and placed at 37°C overnight. After the overnight incubation of the cells, the growth media is removed and replaced with GIBCO EC-SFM. The cells are treated with the appropriate dilutions of the protein of
25 interest or control protein sample(s) (prepared in SFM) in triplicate wells with additional bFGF to a concentration of 10 ng/ml. Once the cells have been treated with the samples, the plate(s) is/are placed back in the 37°C incubator for three days. After three days 10 ml of stock alamar blue (Biosource Cat# DAL1100) is added to each well and the plate(s) is/are placed back in the 37°C incubator for four hours. The
30 plate(s) are then read at 530nm excitation and 590nm emission using the CytoFluor fluorescence reader. Direct output is recorded in relative fluorescence units.

Alamar blue is an oxidation-reduction indicator that both fluoresces and changes color in response to chemical reduction of growth medium resulting from cell growth. As cells grow in culture, innate metabolic activity results in a chemical reduction of the immediate surrounding environment. Reduction related to growth causes the indicator to change from oxidized (non-fluorescent blue) form to reduced (fluorescent red) form. i.e. stimulated proliferation will produce a stronger signal and inhibited proliferation will produce a weaker signal and the total signal is proportional to the total number of cells as well as their metabolic activity. The background level of activity is observed with the starvation medium alone. This is compared to the output observed from the positive control samples (bFGF in growth medium) and protein dilutions.

Example 58: Detection of Inhibition of a Mixed Lymphocyte Reaction

This assay can be used to detect and evaluate inhibition of a Mixed Lymphocyte Reaction (MLR) by gene products (e.g., isolated polypeptides). Inhibition of a MLR may be due to a direct effect on cell proliferation and viability, modulation of costimulatory molecules on interacting cells, modulation of adhesiveness between lymphocytes and accessory cells, or modulation of cytokine production by accessory cells. Multiple cells may be targeted by these polypeptides since the peripheral blood mononuclear fraction used in this assay includes T, B and natural killer lymphocytes, as well as monocytes and dendritic cells.

Polypeptides of interest found to inhibit the MLR may find application in diseases associated with lymphocyte and monocyte activation or proliferation. These include, but are not limited to, diseases such as asthma, arthritis, diabetes, inflammatory skin conditions, psoriasis, eczema, systemic lupus erythematosus, multiple sclerosis, glomerulonephritis, inflammatory bowel disease, crohn's disease, ulcerative colitis, arteriosclerosis, cirrhosis, graft vs. host disease, host vs. graft disease, hepatitis, leukemia and lymphoma.

Briefly, PBMCs from human donors are purified by density gradient centrifugation using Lymphocyte Separation Medium (LSM[®], density 1.0770 g/ml, Organon Teknika Corporation, West Chester, PA). PBMCs from two donors are adjusted to 2×10^6 cells/ml in RPMI-1640 (Life Technologies, Grand Island, NY)

supplemented with 10% FCS and 2 mM glutamine. PBMCs from a third donor is adjusted to 2×10^5 cells/ml. Fifty microliters of PBMCs from each donor is added to wells of a 96-well round bottom microtiter plate. Dilutions of test materials (50 μ l) is added in triplicate to microtiter wells. Test samples (of the protein of interest) are added for final dilution of 1:4; rhuIL-2 (R&D Systems, Minneapolis, MN, catalog number 202-IL) is added to a final concentration of 1 μ g/ml; anti-CD4 mAb (R&D Systems, clone 34930.11, catalog number MAB379) is added to a final concentration of 10 μ g/ml. Cells are cultured for 7-8 days at 37°C in 5% CO₂, and 1 μ C of [³H] thymidine is added to wells for the last 16 hrs of culture. Cells are harvested and thymidine incorporation determined using a Packard TopCount. Data is expressed as the mean and standard deviation of triplicate determinations.

Samples of the protein of interest are screened in separate experiments and compared to the negative control treatment, anti-CD4 mAb, which inhibits proliferation of lymphocytes and the positive control treatment, IL-2 (either as recombinant material or supernatant), which enhances proliferation of lymphocytes.

One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof.

It will be clear that the invention may be practiced otherwise than as particularly described in the foregoing description and examples. Numerous modifications and variations of the present invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

The entire disclosure of each document cited (including patents, patent applications, journal articles, abstracts, laboratory manuals, books, or other disclosures) in the Background of the Invention, Detailed Description, and Examples is hereby incorporated herein by reference. Further, the hard copy of the sequence listing submitted herewith and the corresponding computer readable form are both incorporated herein by reference in their entireties. Additionally, the specifications and sequence listings of U.S. Provisional Application Nos. 60/270,658 and 60/304,444, filed February 23, 2001 and July 12, 2001, respectively, are hereby incorporated by reference in its entirety.

670

**INDICATIONS RELATING TO A DEPOSITED MICROORGANISM
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B. IDENTIFICATION OF DEPOSIT

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PTA-3101

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AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

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UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

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B. IDENTIFICATION OF DEPOSIT

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10801 University Boulevard

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United States of America

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Accession Number

PTA-3102

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NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ATCC Deposit No.: PTA-3102**UNITED KINGDOM**

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

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NETHERLANDS

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PTA-3103

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The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ATCC Deposit No.: PTA-3103

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

What Is Claimed Is:

1. An isolated nucleic acid molecule comprising a polynucleotide having a nucleotide sequence at least 95% identical to a sequence selected from the group
5 consisting of:

(a) a polynucleotide fragment of SEQ ID NO:X or a polynucleotide fragment of the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;

10 (b) a polynucleotide encoding a polypeptide fragment of SEQ ID NO:Y or a polypeptide fragment encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;

(c) a polynucleotide encoding a polypeptide domain of SEQ ID NO:Y or a polypeptide domain encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;

15 (d) a polynucleotide encoding a polypeptide epitope of SEQ ID NO:Y or a polypeptide epitope encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;

(e) a polynucleotide encoding a polypeptide of SEQ ID NO:Y or the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID
20 NO:X, having biological activity;

(f) a polynucleotide which is a variant of SEQ ID NO:X;

(g) a polynucleotide which is an allelic variant of SEQ ID NO:X;

(h) a polynucleotide which encodes a species homologue of the SEQ ID NO:Y;

25 (i) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h), wherein said polynucleotide does not hybridize under stringent conditions to a nucleic acid molecule having a nucleotide sequence of only A residues or of only T residues.

2. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding a secreted protein.

5 3. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding the sequence identified as SEQ ID NO:Y or the polypeptide encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X.

10 4. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises the entire nucleotide sequence of SEQ ID NO:X or the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X.

15 5. The isolated nucleic acid molecule of claim 2, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.

20 6. The isolated nucleic acid molecule of claim 3, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.

25 7. A recombinant vector comprising the isolated nucleic acid molecule of claim 1.

8. A method of making a recombinant host cell comprising the isolated nucleic acid molecule of claim 1.

30 9. A recombinant host cell produced by the method of claim 8.

10. The recombinant host cell of claim 9 comprising vector sequences.

11. An isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence selected from the group consisting of:

(a) a polypeptide fragment of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

5 (b) a polypeptide fragment of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z, having biological activity;

(c) a polypeptide domain of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

10 (d) a polypeptide epitope of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

(e) a secreted form of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

(f) a full length protein of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

15 (g) a variant of SEQ ID NO:Y;

(h) an allelic variant of SEQ ID NO:Y; or

(i) a species homologue of the SEQ ID NO:Y.

12. The isolated polypeptide of claim 11, wherein the secreted form or the full length protein comprises sequential amino acid deletions from either the C-terminus or the N-terminus.

20

13. An isolated antibody that binds specifically to the isolated polypeptide of claim 11.

25 14. A recombinant host cell that expresses the isolated polypeptide of claim 11.

15. A method of making an isolated polypeptide comprising:
(a) culturing the recombinant host cell of claim 14 under conditions
30 such that said polypeptide is expressed; and

(b) recovering said polypeptide.

16. The polypeptide produced by claim 15.

17. A method for preventing, treating, or ameliorating a medical condition, comprising administering to a mammalian subject a therapeutically effective amount
5 of the polypeptide of claim 11 or the polynucleotide of claim 1.

18. A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:

- (a) determining the presence or absence of a mutation in the
10 polynucleotide of claim 1; and
- (b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or absence of said mutation.

19. A method of diagnosing a pathological condition or a susceptibility to
15 a pathological condition in a subject comprising:

- (a) determining the presence or amount of expression of the polypeptide of claim 11 in a biological sample; and
- (b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or amount of expression of the
20 polypeptide.

20. A method for identifying a binding partner to the polypeptide of claim 11 comprising:

- (a) contacting the polypeptide of claim 11 with a binding partner; and
- 25 (b) determining whether the binding partner effects an activity of the polypeptide.

21. The gene corresponding to the cDNA sequence of SEQ ID NO:Y.

30 22. A method of identifying an activity in a biological assay, wherein the method comprises:

- (a) expressing SEQ ID NO:X in a cell;

- (b) isolating the supernatant;
- (c) detecting an activity in a biological assay; and
- (d) identifying the protein in the supernatant having the activity.

5 23. The product produced by the method of claim 20.

<110> Human Genome Sciences, Inc.

<120> 83 Human Secreted Proteins

<130> PS735PCT

<150> 60/270,658

<151> 2001-02-23

<150> 60/304,444

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 <223> Synthetic primer complementary to human genomic EGR-1 promoter sequence (Sakamoto et al., Oncogene 6:867-871 (1991)); includes a Xho I restriction site.

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 <223> Synthetic promoter for use in biological assays; includes NF-KB binding sites.

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| | | | | | | |
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| ccacgcgtcc | gctcctggcg | tgggcaaggc | tggccaagga | tggcgacgcc | cagtggcctg | 60 |
| ggggccctgc | tctgtctcct | cctgctcccc | acctcaggtc | aggaaaagcc | caccgaaggg | 120 |
| ccaagaaaca | cctgcctggg | gagcaacaac | atgtacgaca | tcttcaactt | gaatgacaag | 180 |
| gcttttgtgt | tcaccaagtg | caggcagtcg | ggcagcgact | cctgcaatgt | ggaaaacttg | 240 |
| cagagatact | ggctaaacta | cgaggcccat | ctgatgaagg | aaggtttgac | gcagaagggtg | 300 |
| aacacgcctt | tcttgaaggc | tttgggtccag | aacctcagca | ccaacactgc | agaagacttc | 360 |
| tattttcttc | tggagccctc | tcaggttccg | aggcagggtga | tgaaggacga | ggacaagccc | 420 |
| cctgacagag | tgcgacttcc | caagagcctt | tttcgatccc | tgccaggcaa | caggtctgtg | 480 |
| gtccgcttgg | ccgtcaccat | tctggacatt | ggtccaggga | ctctcttcaa | gggtgaggact | 540 |
| cagggaagct | ccaaggttaa | gtgctaggtc | ctctgggggc | tccatgccac | agtttgctgt | 600 |
| cactggagcc | tgccgagggg | tccaatgggg | acagagcagg | cagtgagcct | cttagtggtt | 660 |
| ctaattgcagc | ccgtggccat | ctcagacacc | tgctactaga | gtctatggtc | ttcagactca | 720 |
| cactggtcac | acgctctcag | atgtttgacc | cccacacatg | agtgcccttt | ggcttgtcta | 780 |
| tgtgtctctg | gggtgctcgt | gtgctctgtg | tgtcctcgctg | catgcacaaa | catgcacatc | 840 |
| cttttctatt | cttgtgcacg | cacaagccca | tgtactcagc | tgtgatcata | tccacacgag | 900 |
| caagtgtacc | catgcccttg | cacatgtgta | taccagggtat | gtgcacccag | aggtgtgcat | 960 |
| ccactcctgt | gcagacgtgt | gtacccttga | gggctagtgt | gctcccccca | ccagcctcct | 1020 |
| ttctaccgaa | tgcacactca | cgctaagacc | ctcaggggca | cgctatcctc | cccgtgact | 1080 |
| tccatttctt | ggctgatctt | ggccccatgc | cccctctagt | taagagggca | gaggagctct | 1140 |
| ggaggccagc | aatggagagc | tgtcagggtg | acagctttgc | agccagttga | cctggcccag | 1200 |
| cccaagcagg | agaccactgg | gagcagcagg | gaggaggctg | cctgtgactc | cttgggtccc | 1260 |
| tgggtccctg | gtctcgaact | ctgccctcca | agcaaaggcc | atgggttctt | ggaggctcct | 1320 |
| aggaaaccca | gcgttggtgg | gttgggatgg | ccccttctgc | agcctggcct | ccccgatctc | 1380 |
| ccctttcaca | gggcccccg | ctcggcctgg | gagatggcag | cggcgtgttg | aacaatcgcc | 1440 |
| tgggtgggtt | gagtgtggga | caaatgcatg | tcaccaagct | ggctgagcct | ctggagatcg | 1500 |
| tcttctctca | ccagcgaccg | ccccctaaca | tgacctcac | ctgtgtattc | tgggatgtga | 1560 |
| ctaaagggac | cactggagag | tgggtcttctg | agggctgctc | cacggagggtc | agacctgagg | 1620 |
| ggaccgtgtg | ctgctgtgac | cacctgacct | ttttcgccct | gctcctggct | ttcccgggag | 1680 |
| aggttcaagt | cagaagatgc | cccaaagatc | cacgaggcct | cgctcggcag | cctgttcctc | 1740 |
| ctgaatctgg | ccttcttggg | caatgtgggg | agtggctcaa | aggggtctga | tgtgccttgc | 1800 |
| tgggcccggc | gcgctgtctt | ccactacttc | ctgctctgtg | ccttcacctg | gatgggcctt | 1860 |
| gaagccttcc | acctctacct | gctcgtctgtc | aggtcttcca | acacctactt | cgggcactac | 1920 |

| | | | | | | |
|-------------|-------------|-------------|------------|-------------|-------------|------|
| ttcctgaagc | tgagcctggt | gggctggggc | ctgcccgcgc | tgatggtcat | cggcactggg | 1980 |
| agtgcccaaca | gctacggcct | ctacaccatc | cgtgataggg | agaaccgcac | ctctctggag | 2040 |
| ctatgctggt | tccgtgaagg | gacaaccatg | tacgccctct | atatcaccgt | ccacggctac | 2100 |
| ttcctcatca | ccttctctct | tggcatggtg | gtcctggccc | tgggtggtctg | gaagatcttc | 2160 |
| accctgtccc | gtgctacagc | ggtcaaggag | cgggggaaga | accggaagaa | ggtgctcacc | 2220 |
| ctgctggggc | tctcgagcct | ggtgggtgtg | acatgggggt | tggccatctt | caccccggtg | 2280 |
| ggcctctcca | ccgtctacat | ccttgcaact | ttcaactcct | tgcaagggtg | cttcatctgc | 2340 |
| tgctgggttca | ccatccttta | cctcccaagt | cagagcacca | cagtctcctc | ctctactgca | 2400 |
| agattggacc | aggcccaactc | cgcattctcaa | gaataggaag | gcacggccct | gcaatatgga | 2460 |
| ctcagctctg | gctctctgtg | tgaccttggg | cagctccgtg | cctctctctg | tactccctca | 2520 |
| gtttctctct | ctgtacaatg | tggctgggga | gggagaggat | gggaccaggt | tggaccaggt | 2580 |
| ggcatcagag | gtcccatcca | gatccaacta | taggtccaag | agtccacgta | agcaggtttg | 2640 |
| caaggctcta | aagtctctat | agtcttgaga | ccccctgcca | gcaaagagtg | acagtcacct | 2700 |
| ccatgccctg | ccctcattgc | aaagccctca | ctcaccttct | ggtctcagca | agggaggaga | 2760 |
| gtctgttgct | ggcatagccc | tgggaaggagc | ccccagcctc | tccccctctc | ctccttgtca | 2820 |
| ctggcctccc | acaactcccc | ttctggctgc | ctgtaacctt | gaggggcatt | caggaggcca | 2880 |
| gcgttccctc | aggcactggg | ggtttgtttt | gggggggtgg | agttgatcct | cccaccagt | 2940 |
| ctgccccctg | tctctgcccc | tccaatcaga | gcccaccctc | ctggaagaga | ccccctgtgt | 3000 |
| cagagtgtctg | gcagccctgc | acgtgtccag | ggacactgca | tttcaaagaa | ccactgagtg | 3060 |
| ggtgagctac | cttgggcaaa | ccccccactc | ctgactctga | ctgccacgtg | ggtggcccgga | 3120 |
| cctctgacct | gctgtcatcg | tagaggtaga | aagcaaacaa | tctggggctc | agcacacctg | 3180 |
| ggggtgctcc | cactcattca | gtgtgtgggg | cccctgagca | gaggctgggc | attgccctca | 3240 |
| ggacctgagc | tcttagagaa | caaggacctg | ggtggcctcg | cttactgttc | cagcccaggc | 3300 |
| caagcacagg | gtctggctcg | tggcaaacct | tgaataaata | tttgttggct | gaaaaaaaaa | 3360 |
| aaaaaaaaaa | a | | | | | 3371 |

<210> 15
 <211> 1214
 <212> DNA
 <213> Homo sapiens

| | | | | | | |
|-------------|-------------|------------|------------|-------------|-------------|------|
| <400> 15 | | | | | | |
| cggggtcgac | ccacgcgtcc | gcgaggacca | gctgtcctgg | ttcgctgccc | tgggtcaagtg | 60 |
| cctgcccgtc | ctctgcctgg | ctgggttcct | gtgggtcatg | tccccaaagc | ggggctacac | 120 |
| ccagctctct | cagggaagccc | ttgtgtgctc | ggctgtgggg | gacgcttgcc | tcacttgccc | 180 |
| ggcagccttc | gtccctggca | tggccgcctt | tgccaccgcc | cacctctctt | acgtctgggc | 240 |
| cttcggcttc | tctcccctgc | agcccggcct | gctgtgtctc | atcatcctgg | ccccctggccc | 300 |
| ctacctcagc | cttgtgtctc | agcacctcga | gccggatatg | gtcctgccgg | tggcagccta | 360 |
| tgggctgatc | ctgatggcca | tgtgtgtggc | cggcctggcc | cagggcgagg | gtgccggctg | 420 |
| ggggcgctg | ctcttcacgc | tctctgatgg | cgtgtgtggc | tgggacacct | tcgcccagcc | 480 |
| cctgccccat | gcccacctgg | tgatcatgac | cacctactat | gctgcccagc | tcctcatcac | 540 |
| actgtcagcc | ctcaggagcc | cgggtgccaa | cagctactga | ctagggaagt | tgaaggggcc | 600 |
| gtgttcaggc | cctctcctcc | tgcaaggacc | tgggcctccc | agcccagccc | agcctgagaa | 660 |
| ataccctcag | cagcgaagct | tcctgacgcc | tgtctgcagg | cgccgctgcc | gccgtcgctt | 720 |
| ctggctgaag | acgtttgagg | acgatttgcg | gaattccaag | tccactactg | ggttccagct | 780 |
| gccttcccc | ggttctgact | ccagatccct | ggctcctcag | ccaggccccac | atggagccct | 840 |
| cccagccacc | agcctgcctc | catgttcact | gtcggcccca | cagcctgccc | gccccctgct | 900 |
| gctgtctctga | atccgttttc | cctgtgggtg | tggaaacgta | gatgttgctg | ttaccgtagg | 960 |
| agaggcctcg | gggagggtca | tgatttgtat | aaaccatcgc | ggttaatgac | agcagaagggt | 1020 |
| tctttgtcgc | tccccatgga | ccaggcctgg | tgcccagtg | gaccctccat | ggccctctgg | 1080 |
| tggggggatt | cggggggata | aagtgaggat | tgtgcagaac | tgaaaaaaaaa | aaaaaaaaaaa | 1140 |
| aaaaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | 1200 |
| aaaaaaaaaa | aaaa | | | | | 1214 |

<210> 16
 <211> 896
 <212> DNA
 <213> Homo sapiens

| | | | | | | |
|-------------|------------|-------------|------------|-------------|------------|-----|
| <400> 16 | | | | | | |
| ccacgcgtcc | gcgaattctg | ctcagctcgc | tttggcagct | tgggtgggagg | tggggcgagg | 60 |
| tggcggaggc | gattgaagct | gctggcccag | catgtggtgc | gcgagcccag | ttgtgtgtgt | 120 |
| ggccttttgc | gccgggcttt | tgggtctctca | cccgggtgct | acgcaggggc | aggaggccgg | 180 |
| ggggcgggcca | ggggccgact | gtgaagtatg | taaagaattc | ttgaaccgat | tctacaagtc | 240 |
| actgatagac | agaggagtta | acttttctgc | ggacactata | gagaaagaat | tgatcagttt | 300 |
| ttgcttggac | accaaaggaa | aagaaaaccg | cctgtgctat | tatctaggag | ccacaaaaga | 360 |

| | | | | | | |
|-------------|------------|------------|-------------|------------|-------------|-----|
| cgcagccaca | aagatcctaa | gtgaagtcac | tcgcccgaatg | agtgtgcata | tgccctgcaat | 420 |
| gaagatttgt | gagaagctga | agaagttgga | tagccagatc | tgtgagctga | aatatgaaaa | 480 |
| aacactggac | ttggcatcag | ttgacctgcg | gaagatgaga | gtggcagagc | tgaagcagat | 540 |
| cctgcatagc | tggggggagg | agtgcagggc | ctgtgcagaa | aaaactgact | atgtgaatct | 600 |
| cattcaagag | ctggccccc | agtatgcagc | gacacacccc | aaaacagagc | tctgatctcc | 660 |
| aatgccagca | catttgtgac | ttgtaattag | agagaaaagt | gactctctag | gatatggaca | 720 |
| tggttgattaa | ggataactgg | gaatgcacat | tatttgggtct | catgaaaaaa | aaaaaaaaaa | 780 |
| aaaaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | 840 |
| aaaaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | aaaaaa | 896 |

<210> 17
 <211> 1299
 <212> DNA
 <213> Homo sapiens

| | | | | | | |
|------------|-------------|-------------|-------------|-------------|------------|------|
| <400> 17 | | | | | | |
| ggcagcagca | accgcctggg | gcccttgccc | ttctggcttc | tctactgctg | ccccgtctgc | 60 |
| ctgcagttct | tcaccttgac | gcttatgaac | ctctactttg | cccaggtggg | gttcaaggcc | 120 |
| aaggtgaagc | gtcggccgga | gatgagccga | ggcttgctcg | ctgtccgagg | ggcctttgtg | 180 |
| ggggcctcgc | tgctctttct | gctggtgaac | gtgctgtgtg | ctgtgctctc | ccatcggcgc | 240 |
| cgggcacagc | cctgggccct | gctgcttgct | cgcgtcctgg | tgagcgactc | cctgttcgtc | 300 |
| atctgcgcgc | tgtctcttgc | tgccctgcctc | tgccctgcctc | ccaggcgggc | gccctccact | 360 |
| agcatctacc | tggaggccaa | ggggaccagt | gtgtgccagg | cggccgcgat | gggtggcgc | 420 |
| atggtcctgc | tctatgccag | ccgggcctgc | tacaacctga | cagcactggc | cttggccccc | 480 |
| cagagccggc | tggacacctt | cgattacgac | tgggtacaatg | tgtctgacca | ggcggacctg | 540 |
| gtgaatgacc | tggggaacaa | aggctacctg | gtatttggcc | tcctctctct | cgtgtgggag | 600 |
| ctactgcccc | ccacctgtgt | ggtgggcttc | ttccgggtgc | accggccccc | acaggacctg | 660 |
| agcaccagcc | acatcctcaa | tgggcagggtc | tttgccctctc | ggtccctactt | ctttgaccgg | 720 |
| gctgggcact | gtgaagatga | gggctgctcc | tgggagcaca | gccgggggtga | gagcaccagt | 780 |
| atgtcgggca | gtctagctgc | tgggagctgg | tatggtgcc | tcgggcgtga | gccgggctgg | 840 |
| tatgggggca | gccagacgaa | gaccactcct | ctgctcttct | cccagggtgc | aggaccaggc | 900 |
| ggccaccacc | acagtctcta | ctccacccca | cagacgtgat | ccccctccct | ccccacaga | 960 |
| ataccagggc | cccagtcctc | ctcaccctag | gcccctgtgc | caagtttgtc | tgccgcttct | 1020 |
| tgcccaggat | cctgggggtc | gtggctaccc | cctcctctgg | ccggctcctt | gctgctcctg | 1080 |
| tcatagtgag | cttgtgcccgt | ccccctagga | tggggggcat | ggccctgggt | gccagatgcc | 1140 |
| cacagcacc | tggcagacc | tgccacctct | gcttcacac | cggagccagc | tacctctcct | 1200 |
| gtgcctgcca | ctcaataaac | agtgtctgcg | ccccacaaaa | aaaaaaaaaa | aaaaaaaaaa | 1260 |
| aaaaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | | | 1299 |

<210> 18
 <211> 1796
 <212> DNA
 <213> Homo sapiens

| | | | | | | |
|------------|------------|------------|-------------|------------|-------------|------|
| <400> 18 | | | | | | |
| ggcagcaggt | cggagaagag | ataccctcag | ccacggggcc | agaagaagaa | gaaagtgggtg | 60 |
| aagtatggca | tgggaggaat | gatcatcgct | ctgctcatct | gcattgtctg | gtttcctctt | 120 |
| ctcttcatgt | ctttgatcaa | atctgtggct | gggggtcatca | accagccctt | ggacgtctcc | 180 |
| gtcacaatta | ccctgggagg | gtatcagcct | attttcaca | tgagtgccca | acaaagccag | 240 |
| ttgaaaatta | tggaccagca | gagctttaac | aaatttatac | aagctttttc | tagggacacc | 300 |
| ggtgctatgc | aatttctgga | aaattatgaa | aaagaagaca | taacagtagc | agaactggaa | 360 |
| ggaaactcaa | attctttgtg | gaccatcagc | ccaccagta | agcagaaaa | gatacacgaa | 420 |
| ctcctggacc | ccaatagtag | cttctctggt | gttttttcat | ggagtattca | gagaaactta | 480 |
| agtctgggtg | caaaatcgga | aataagcaac | gataagcttt | cttttctctt | taaaaatatt | 540 |
| aactcgaaag | aatatcgcta | aatgatagc | aggcaacagc | acagaaagtt | caaaaacacc | 600 |
| agtgaccata | gaaaagattt | atccatatta | tgtgaaagca | cctagtgtat | ctaactcaaa | 660 |
| acctataaag | caacttttat | ctgaaaataa | tttcatggat | attaccatca | ttttgtccag | 720 |
| agacaatata | actaaatata | acagtgtgtg | gtgggttctc | aacctgactg | gaaacagaat | 780 |
| atacaatccg | aactctcagg | ccctggaact | ggtgggtctc | aatgacaaag | tcagtcctcc | 840 |
| aagtctgggg | ttcctggctg | gctatgggat | tatgggatta | tatgcttcag | ttgtccttgt | 900 |
| gattgggaaa | tttgtccgtg | aattcttcag | tgggatttct | cactccatca | tgtttgaaga | 960 |
| gcttccaaat | gtggatcgaa | ttttgaagtt | gtgcacagat | atttttttag | ttcgagagac | 1020 |
| aggagaactg | gagctagaag | aagatctcta | tgccaaatta | atattcctat | atcgctcacc | 1080 |
| agagacaatg | atcaaatgga | ctagagaaaa | aacaaattga | aaccttagaa | cacagactgc | 1140 |
| aaataatgtt | aacatttgaa | ttttttttta | aagcacaata | ttctcataag | agctaagcat | 1200 |
| ttctagtctg | acggaaatgg | tttgtttctc | ttctgatagg | tagacaaaag | gagctgatat | 1260 |

| | | | | | | |
|-------------|------------|------------|------------|------------|------------|------|
| cctttctgcag | taaaagctac | cttgcaagtt | aaggcactgt | tgaaaatggt | atgtgtaact | 1320 |
| ccattttctct | gaaatcaggg | ctacttgctt | tatgttttag | tcaacagtgt | ctcgcattct | 1380 |
| gattgatcat | gtgaaggaat | catttatggg | ccccgtccct | aagagaaaca | gaagaggagt | 1440 |
| cagaaagaaa | gatgcctgtg | ttttcctctg | tggggcccg | gcacttcctg | gagagatgct | 1500 |
| acaatgcaat | atacagcgct | ccatccccac | tggggaagct | gctgtgatga | gactagatga | 1560 |
| gccttcaaca | cactcagaaa | atgcaacagc | aatagggggc | agacagctcc | tacctgtgtt | 1620 |
| tctaggagca | aaagagaggg | aactaattgc | ccgtgaagac | gccagtggaa | ggatcagcct | 1680 |
| cattctaagc | aaaaacatag | tattagtgat | actcttactg | ccttatctta | accaaggact | 1740 |
| aataggatac | ctttccatta | aacaccagtg | acttctcagg | aaaaaaaaaa | aaaaaa | 1796 |

<210> 19
 <211> 1881
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (1865)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (1873)
 <223> n equals a,t,g, or c

| | | | | | | |
|------------|-------------|-------------|-------------|-------------|-------------|------|
| <400> 19 | | | | | | |
| gaattcggca | gagggtagg | cccaggtagc | gtttgcaatc | cagccccacc | gtcacctctt | 60 |
| ttcttggact | tctagttttc | ctcaccctta | ttgccttcat | cctttttacct | ccgatcctgt | 120 |
| ggagggatga | gctggagcct | tgtggcacia | tttgraggg | gctctttatc | tccatggcat | 180 |
| tcaaatcctc | cattctgctc | atagggacct | gggcactttt | ttccgcaag | cggagagctg | 240 |
| acatgccacg | ggtgtttgtg | tttcgtgccc | ttttgttggg | cctcatcttt | ctctttgtgg | 300 |
| tttccatttg | gcttttttac | ggggtccgca | ttttggactc | tcgggaccgg | aattaccagg | 360 |
| gcattgtgca | atatgcagtc | tcccttgtgg | atgccctcct | cttcatccat | tacctggcca | 420 |
| tcgtcctgct | ggagctcagg | cagctgcagc | ccatgttcac | gctgcagggtg | gtccgctcca | 480 |
| ccgatggcga | gtcccgcctt | tacagcctgg | gacacctgag | tatccagcga | gcagcattgg | 540 |
| tggctcctga | aaattactac | aaagatttca | ccatctataa | cccaaaccct | ctaacagcct | 600 |
| ccaaattccg | agcagccaag | catatggccg | ggctgaaagt | ctacaatgta | gatggcccca | 660 |
| gtaacaatgc | cactggccag | tcccgggcca | tgattgctgc | agctgctcgg | cgcaggggact | 720 |
| caagccacaa | cgagttgtat | tatgaagagg | ccgaacatga | acggcgagta | aagaagcgga | 780 |
| aagcaaggct | ggtgggttgca | gtggaagagg | ccttcatcca | cattcagcgt | ctccaggctg | 840 |
| aggagcagca | gaaagcccca | ggggagggtga | tggaccctag | ggaggccgccc | caggccattt | 900 |
| tcccctccat | ggccagggct | ctccagaagt | acctgcgcag | caccgggcag | cagaactacc | 960 |
| acagcatgga | gagcatcctg | cagcacctgg | ccttctgcat | caccaacggc | atgaccccca | 1020 |
| aggccttcc | agaacggtac | ctcagtgcgg | gccccaccct | gcaatatgac | aaggaccgct | 1080 |
| ggctctctac | acagtggagg | cttgtcagtg | atgaggctgt | gactaatgga | ttacgggatg | 1140 |
| gaattgtgtt | cgctccttaag | tgcttggact | tcagcctcgt | agtcaatgtg | aagaaaattc | 1200 |
| cattcatcat | actctctgaa | gagttcatag | accccaaattc | tcacaaattt | gtccttcgct | 1260 |
| tacagtctga | gacatccggt | taaaagtctt | atatttgttg | ctttattaaa | aaaaaaaaaa | 1320 |
| aaatatatat | agagatatat | atctatgcca | gaggggtgtc | ttttttaaaa | attcttcttc | 1380 |
| attgctgact | gaaactggca | gatgattgac | cagtatcctt | tgaccatctg | cactttattt | 1440 |
| ggaaggaagc | aggggctgtc | caccctgaaa | aagagtgtg | gatgacatct | gacttttgtc | 1500 |
| gatgggactt | ctcaagaagc | cattccttgg | agcttctgtt | acagctgtaa | accaaagtgg | 1560 |
| agctggtgct | tcttgggagc | ctcgccttac | aactagtgtc | tgcttttcgt | ccagtaccaa | 1620 |
| gtcccccggt | gcttctgggt | agcccacttg | tagacttcca | ggggacacat | ctttattctg | 1680 |
| tttcaggaaa | ccagtcacra | cacgtccaca | tatgtatttg | tgtatgttaa | tgccagtatc | 1740 |
| acatcaccca | tgaaagtcgt | gggcagttca | rgagatacct | gscttcgtct | ttgktctttg | 1800 |
| ttgccttagg | ttcttcagag | aaagatcmca | acaaaaaatg | tacmctgtcg | tttacagcta | 1860 |
| waagnatttt | ganttggtttt | t | | | | 1881 |

<210> 20
 <211> 2618
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE

<222> (2597)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (2599)
 <223> n equals a,t,g, or c

<400> 20

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| tgtggggcaat | accggttact | atcattatct | gtttttcttg | gcttgaatat | tctcagactt | 120 |
| gggcttttggg | tgcttcttgg | agtttgccgc | aatgcccttt | tgatgtgatg | ctatcattat | 180 |
| ttttagtaca | tccttacttt | ccaacagtat | gggatcatct | ttgttttccc | catcccagtc | 240 |
| ctgaaagtag | ccctttctcc | aagtgttcac | tggttgcttg | gttgaggaaat | ggtgcatagg | 300 |
| aaccaagatc | tgagtgcag | ggtgctcttc | actgttggga | tgatcattgct | tctgggtgtg | 360 |
| ttggagccag | caaatatata | tatgtacact | aattcatgca | tgcacacatt | tgcatttatt | 420 |
| tatacatcta | tccatctgcg | tgtgtatacg | tgtgtgtata | tgtgttacca | tgagttaata | 480 |
| ccaattactc | tgatttcaat | ccaacacaat | gggttctttc | taattatctt | taatttctct | 540 |
| caaaatcact | tcttctgggt | cttccagaaa | atgagctctt | cacctagctt | aagaatgtag | 600 |
| agatgtcgtg | tatgggttggg | cagggtgttc | actgtccaag | ggtgttccag | ctgaggagag | 660 |
| cgatgggagc | tgaaagcatc | catgctctac | tccctaagct | ctgcactcta | acatgtgctc | 720 |
| tgggtccacc | agagtaaggg | atgccctctt | ttcacttgtg | caaatgcact | gggtgagcta | 780 |
| gcaacagacc | tggtcgactg | ctgtctcggg | atatttttgt | gtttacttgt | gaaacaccca | 840 |
| ggcttgggct | ggattccccc | agaggcagat | tgtgagctga | ggatttgagt | gcgaggagta | 900 |
| ttttgggatg | tgattccagg | aacctcccag | agagaagcag | tggggagtc | ggcaggaaag | 960 |
| aaagcatgcg | tcaggggagct | ggttactact | gggccaccga | ggctccatcc | cagtaaggaa | 1020 |
| ccctggaaga | cgggaggaac | gcaccttggg | gttgcttccc | taagggatca | acttcagttg | 1080 |
| gtcgccactc | aaggctcctc | ctgaggggag | caggcacaga | gtccctggca | cttctggccc | 1140 |
| tgagtgcctc | ggggatgagt | gcgtgacatt | gacggcttct | gctgtcctct | gtctcctgct | 1200 |
| ttccccgtgg | gatgaactag | cttgagaggc | acaagattcc | tgagcaggca | gagggactct | 1260 |
| gtaggagtct | cagagctcct | gaggctgcac | cctgcctctg | gagccccgtg | aaatcttcaa | 1320 |
| ttttgggttt | tatgagcttc | acaaaccttc | caggggcctc | tccggctccg | gatgggggtgc | 1380 |
| gttgagggcc | tggtgcccac | gtgtctcctg | ggccctccac | ctgtgccccg | cctgttttgc | 1440 |
| cagtgtgctg | gagctgagca | cctgagtttg | ctctttgaat | caagtgttta | actcactcac | 1500 |
| ggtaatatgt | gctgataatt | cttgagctaa | cacaccttct | actttgcggc | ctagccttgt | 1560 |
| ttgcctttca | gccctgggtt | attatcttcc | atcggatgaa | gcttaggagc | accagcgtg | 1620 |
| cctagggaaa | ccctggcccc | tccttccctg | ggatcatctg | ggteccccag | ggctcaggct | 1680 |
| ttacaacccc | tgctgcttgg | ttaccacact | cccacctggg | gcccctgaca | gatcagggga | 1740 |
| caagcagata | gagggctcac | cagtgcagtc | cagtgtatgc | tgccgggagg | gccggagcag | 1800 |
| agtgagtcag | atgttgcttt | ttataatcat | ccagggtgcca | gggtgggcac | gcgtcctggg | 1860 |
| tcacctcttc | agcgagggtc | cacatcatag | cctgtcacca | gcagtaattc | agcaggaggg | 1920 |
| tttagtttcc | tccctatggg | atcagcgagg | gcagctgtct | aagccccagg | cacactgcct | 1980 |
| agggcgagag | tggggggtgg | ggcgcctcct | ctagggtgct | cctgcctctt | ggcagggtgat | 2040 |
| cagccttcac | ctccttgtgt | ggtttagggg | ggctgcctcc | tgtctatgtc | agagggcttc | 2100 |
| tcagaaacag | gcaccgctgt | aggggcagca | agatgacttc | acttggaata | tggaatgtac | 2160 |
| ttaaacgaga | tcaagccacc | tcgtggagaa | gccattccct | tccaatttgt | tttaattcctg | 2220 |
| ctgattattg | caaagagaaa | gacttagcct | gggtgctaag | agtctttaat | gcctctgagg | 2280 |
| acttcttaag | tttctctttt | ttttctaaac | aagaaaagtt | aagcctcagg | ctgttcatcc | 2340 |
| ttctagttgg | aatttaataa | ccgtgttttg | ttttcataga | atttaccttt | ggagttgttt | 2400 |
| attcatggca | gggcctcctg | gttttccatt | ttggggagtg | ataggaagtt | ttccattaaa | 2460 |
| ttaatatttt | gtatatattt | ttttacagtg | agtccttaat | atattttgta | ggtaatatga | 2520 |
| tgggtgaggt | tggcaacta | tggccctggg | ctaaatctag | tgtatagcat | gtttttgtca | 2580 |
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<210> 21
 <211> 1549
 <212> DNA
 <213> Homo sapiens

<400> 21

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| gcttcatagt | gtatattttc | tctattccat | taaatttaat | taatttcatt | tgattttatt | 120 |
| ctgttcttca | ggaatcttag | tttttatata | gtccaactca | tgtactctgc | ttccgtcatt | 180 |
| aagaattcat | agtgggagaa | ataggctgtt | gcctttttct | tagaatgcat | ggggcaaggc | 240 |
| tgtttgtttg | tttgtttgtt | tgcttttagc | agtcttgcta | tgttgcccag | gctggagtgc | 300 |
| agtggcacaa | tcacagctca | ctgcaacctc | tgtctcccgg | gttcaagaga | ttcttctgcc | 360 |

| | | | | | | |
|-------------|-------------|-------------|------------|-------------|-------------|------|
| tcaacctccc | gagtagctgg | gattacaggg | acatggcaac | atgccccctgg | ctaattttttg | 420 |
| tattttttagt | agagatggag | tttcgcctatg | ttggccaggc | tggtctttgga | ctcctgacct | 480 |
| caagtgatct | gcctgccttg | gccttccaaa | gtgctgggat | tacaggactg | agccaccacg | 540 |
| cctggccagg | gcgtttttctt | aaaaaagtga | ttgaaatctg | ctcatgccct | gtgccacgtg | 600 |
| ggtctcacgc | aggtctgttc | tctgtctccag | gtctgccatg | tgaatctgga | ggggcagccg | 660 |
| ttctactcca | agaaggacag | accctgtgct | aagaagcacg | cacacaccat | caacttgtag | 720 |
| gcgcccaagg | ccgcctgtgc | tgacgaggcc | cggagctgct | cctgctgctg | gcaacaaagg | 780 |
| attcgggagg | ctgatgtttc | ttctgagggg | aatggggaga | gagaggaagc | gactgagccc | 840 |
| tttggaagta | taatttttagg | ttttttcttc | tgtacacaga | tcgtgcattt | gcatagttca | 900 |
| gactaggagc | caaatgaaga | ctcaaaaacca | agctagtatt | taatccaaga | ctggaattgt | 960 |
| acttcagaca | tttagagcag | aattccaaga | actcaaaagt | gaaaagcaac | aagcagcttt | 1020 |
| cccaaagcga | tacacttgct | ttggtcacca | gaggaggaca | gagcttagag | cagctgtgga | 1080 |
| gaatctgaag | cattctgcgg | agttcttaag | cgctcccttg | gcaaacaat | tgaagtgcc | 1140 |
| aacagcactc | gctgcaggg | attttttagag | tcatagtgga | gagcttggtta | gctaagacct | 1200 |
| attgggcttt | cctcaccaaa | aaaggaagtg | ttattccatt | actagcgtca | tggagctacc | 1260 |
| tctgcgcata | agacttcaga | ccttgaacaa | acttaaaacc | ttcttgggag | ccgggacgtc | 1320 |
| caaagagatg | tcttctggga | gccactgggc | aattgccagg | gctccaggaa | gggctctggc | 1380 |
| tcaggttgca | gacagctgag | aaaagatggc | cctgtcagcc | accctctctc | agtctgaaac | 1440 |
| atccaacatc | cccagaaggc | ttagctcctt | tttgaattgt | gatgggaaag | tagagttggg | 1500 |
| tttttctctg | tgccgaattc | gatatcaagc | ttatcgatac | cgctgacct | | 1549 |

<210> 22

<211> 3239

<212> DNA

<213> Homo sapiens

<400> 22

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| gatggcacct | gccggctgct | gctgctgctg | ctgcttctgg | ggcggcgctg | tggccgcgcg | 120 |
| gggcgcgcgc | cggcgtgtcc | tgctgctgct | gctgttgggg | gtcctgtccg | cccggctgcg | 180 |
| gccaggcgcc | ctggccaccg | agcactactc | gccgctcgcc | ctgctcaagc | aggagctgca | 240 |
| gcaccggcag | cagcaggagg | ccccggcggg | cggcggcgcc | tgcagccgcg | agtccgggga | 300 |
| ctggggggac | cagtactctg | ccgagtgcgg | cgagtcatcc | tttttgaact | tccatgactc | 360 |
| agactgcgaa | cccaagggat | catcaccttg | tgactccttg | ctttccctca | acactgagaa | 420 |
| gattctgagc | caggccaagt | ctattgcaga | acagaagaga | ttcccgtttg | ccactgataa | 480 |
| tgacagcaca | aatgaagagt | tagctattgc | ttatgtcttg | attggcagtg | gtctgtatga | 540 |
| tgaagcaata | cggcattttt | caacaatgct | tcaggaggag | cctgatctgg | ttagtgcaat | 600 |
| ttatggccga | gggatagcct | atggaaagaa | gggactacat | attctgtccc | ctctgggacg | 660 |
| aattaatgaa | gcagtgaatg | acctactaa | agctatccaa | ctgcagccct | cagcacggct | 720 |
| gtacagacat | cggggaaccc | tgtacttcat | atcagaggac | tatgcaacag | cccatgaaga | 780 |
| ctttcagcag | tccttagaac | tgaacaaaaa | ccagcctata | gctatgctat | acaaagggtt | 840 |
| aactttcttt | cacagaggac | ttctgaagga | agctattgaa | tccttcaaag | aagctttgaa | 900 |
| gcagaaagtt | gactttattg | atgcatataa | aagtctaggg | caggcatata | gagaactggg | 960 |
| caattttgaa | gcagccactg | agagctttca | aaaggcactg | ttgctcaacc | aaaatcatgt | 1020 |
| gcaaaccctc | cagctccggg | gaatgatgct | ctaccaccac | ggcagcttac | aggaagccct | 1080 |
| taagaacttt | aagcgggtgtc | tgcagctaga | gccatataat | gaagtgtgcc | agtatatgaa | 1140 |
| agggctcagc | catgttgcca | tgggacagtt | ttatgaaggg | ataaaagcac | aaacaaaagt | 1200 |
| tatgctgaat | gatacctctc | caggccagaa | ggctagccct | gagtatctta | aagttaaagt | 1260 |
| tctccgagag | tattctcgat | atcttcatgc | acaccttgat | acccccctta | cggaaataaa | 1320 |
| cattgatgtg | gatctgcctg | gaagctttta | ggaccactgg | gctaaaaatt | tgcctttcct | 1380 |
| catagaagac | tacgaagagc | agccagggtt | gcaacccac | ataaaagatg | tgttacatca | 1440 |
| gaattttgag | agttataagc | ctgaagtaca | ggagctgatt | tgtgtggctg | atcgtttggg | 1500 |
| atccctgatg | caatatgaaa | cacctgggtt | cctgccaac | aagagaatac | acagagctat | 1560 |
| gggtttggcc | gcattggagg | tcatgcaagc | cgtgcagcgt | acatggacca | actcgaaagt | 1620 |
| tcgaatgaat | gggaagacac | gggtgatgca | gtggagagac | atgtttgaca | ttgcagttta | 1680 |
| atggagaagg | attgctgacc | cagaccagcc | cgtgctgtgg | ttagatcaaa | tgccagcacg | 1740 |
| aagtcttagc | agagggtttta | acaaccacat | taattttaatc | aggggacagg | tgatcaacat | 1800 |
| gagataccta | gaatattttg | agaaaatact | tcatttttatt | aaagacagaa | ttcttgttta | 1860 |
| tcattggagct | aataactcta | aaggattgct | ggaagtctcg | gaagccctgg | aaaagggtaca | 1920 |
| caaagttagaa | gaccttcttc | cgattatgaa | gcagtttaat | actaaaacga | aggatgggtt | 1980 |
| caccgtgaac | acaaaagttc | ccagccttaa | agaccaaggg | aagggaatatg | atggattcac | 2040 |
| aatcacgatt | acaggagaca | aagttggcaa | tatattatatt | tctgtggaaa | ctcaaaccac | 2100 |
| ggaagaaagg | acacaattat | atcatgctga | aatagatgca | ctttataaag | atttgacagc | 2160 |
| aaaaggaaaa | gtattgatcc | tttcatcaga | atttggggag | gctgatgctg | tctgcaactt | 2220 |
| aatcttatcc | ttagtttatt | acttttataa | tttaatgcc | ctctctcgag | gatccagtg | 2280 |
| aattgcttac | tcggctcatc | tgggagcact | gatggcaagt | ggaaaagaag | tagcaggaaa | 2340 |

| | | | | | | |
|------------|-------------|------------|------------|------------|------------|------|
| aattcccaaa | gggaagttag | tcgactttga | agctatgaca | gcccctgggt | cagaggcctt | 2400 |
| tagcaaagtc | gccaaaagct | ggatgaactt | gaaaagtatt | tcaccttctt | ataagactct | 2460 |
| tccatcagta | tcagaaacgt | ttccaacgtt | aagatcgatg | attgaggtgc | taaacacaga | 2520 |
| ctcttctcca | cggtgtctta | agaaactcta | gttctgctgc | tgtatttata | caagtaaagg | 2580 |
| gccggacctc | ttgcttctta | agttatcttt | ttaaaacatg | gaattataaa | gaaattaggt | 2640 |
| cctctattac | ttttgatacc | aatttttata | ggaattgaat | acttgaaatc | attttcttta | 2700 |
| cttttctgaa | ccataatgaa | aatcatgaaa | gaggctttcg | gggggaaaaa | gctacttgac | 2760 |
| ttggagggaa | agcgtatgta | ttagccggca | gcctgttggt | tcccacttat | aaagtcatat | 2820 |
| aactccttcc | ttacagtata | aaaaattttc | ctcaacaact | aaaatataat | actgaagatg | 2880 |
| aacaaaaaca | aaaccaaaata | ggagtgtttg | tattccttta | gagatctgga | tatttttcaa | 2940 |
| agacttgctt | tttacgcaca | ttgtgataga | gcactttttg | ttgactcacg | taacctccat | 3000 |
| gtgtgggtcc | tttgttttat | tagaaccatg | gaagaagggt | cctgggccat | cagtattgtt | 3060 |
| tgcagagctc | acagccagga | acacttattt | tgaacaatgc | agacagtact | tgccagagtc | 3120 |
| ccaaatgctg | aattattgaa | ccatgttttt | ttttcctttg | ttgaaaaaaa | taaaccaggg | 3180 |
| tgatttctat | aaatcaccag | tttttggcat | tgaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | 3239 |

<210> 23
 <211> 1433
 <212> DNA
 <213> Homo sapiens

| | |
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| gtgaatgaca | agtcaaaatt |
| tggtgcacag | tacagagatg |
| gtccactctg | ccactcacca |
| tcagtttccc | catcggcaag |
| tcccaaattc | aaaatgctcc |
| agcactttgg | gaggtcaaag |
| gccaacatgg | cgaaacccca |
| gggcacctgt | aacccagct |
| cagtgaagctg | agatcacacc |
| caaaaaacaa | aaaaacatgc |
| aagtgggaaa | ttccacaact |
| ccacgaagtt | tactcagcat |
| tcacatgccca | gataggtatc |
| ggaggaaaat | gattgctggg |
| cggctgggtg | cagtggctca |
| gtgattgact | ctcccttagc |
| cagtctctca | cccaccccc |
| tgcgattact | gataagatac |
| ttgatagcac | ccaaagcccc |
| tggaactgtt | tggttttctg |
| tgtaaaattg | cttcagctcg |
| ctagcccctt | ctttgggggtg |
| aataaaggac | tcctgaatta |
| ccagaggtga | atgtattggt |
| tggtgggttat | tggtgttatc |
| aaggaaacag | atthttgcaat |
| gctatatgac | ctccagcaat |
| atgggtgtgg | ggggagagga |
| aaaatctagg | cggggcgtgg |
| tggacggata | acctgaggtc |
| tctctactaa | aaatacaaaa |
| ctgaggcagg | aacctggag |
| actgcactcc | agcctgggtg |
| acagagcaag | gctcccattc |
| gagccccagt | gtgatgccac |
| gatagattgc | agtggaaatg |
| aatccccgct | agtagctata |
| tactgttagg | tacttctgtg |
| ttaaattcaga | gtcaggaagg |
| tccaatgtga | taccctacct |
| tattttggct | tcttcgcttg |
| acttaagctg | actcccagca |
| tatatccaca | gttcccagga |
| accttgtgat | acatttaaag |
| tttttttcac | tttcttgctt |
| accaaaggtat | aaaaagaaac |
| cgtctctca | gtcgccggct |
| aaaaaaaaaa | aaa |

<210> 24
 <211> 2517
 <212> DNA
 <213> Homo sapiens

<220>
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 <222> (950)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (1247)
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| | |
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| gaaaatgaag | tgaatcctga |
| atctaactag | gcatttctat |
| actttaaatg | ctgggtggatt |
| aatactagt | aatcatcat |
| gatgtggctg | cttgatttg |
| cttgatttg | ctacaatggc |

| | | | | | | |
|-------------|-------------|-------------|-------------|------------|-------------|------|
| tacccagtg | aagagtatga | agtcaccact | gaagatgggt | atatactcct | tgtcaacaga | 240 |
| atttccttatg | ggcgaacaca | tgctaggagc | acaggtcccc | ggccagttgt | gtatatgcag | 300 |
| catgccctgt | ttgcagacaa | tgccactagg | cttgagaatt | atgctaattg | aagccttgga | 360 |
| ttcctttctag | cagatgcagg | ttatgatgta | tggtatggaa | acagtcgggg | aaacacttgg | 420 |
| tcaagaagac | acaaaacact | ctcagagaca | gatgagaaat | tctgggcctt | tagttttgat | 480 |
| gaaatggcca | atatgatctc | ccaggagtaa | tagacttcat | tgtaaataaa | actggtcagg | 540 |
| agaaatttga | tttcatttga | cattcacttg | gcactacaat | agggtttga | gccttttcca | 600 |
| ccatgcctga | actggcaca | agaatcaaaa | tgaattttgc | cttgggtcct | acgatctcat | 660 |
| tcaaataatcc | cacgggcatt | tttaccaggt | tttttctact | tccaaattcc | ataatcaagg | 720 |
| ctgttttttg | taccaaaggt | ttcttttttag | aagataagaa | aacgaagata | gcttctacca | 780 |
| aaatctgcaa | caataagata | ctctggttga | tatgtagcga | atttatgtcc | ttatgggctg | 840 |
| gatccaagca | gaaaaatatg | aatcagagtc | atccccctat | atatgacctg | actgccatga | 900 |
| aagtgcctac | tgctatttgg | gctggtggac | atgatgtcct | cgtaacacn | taggatgtgg | 960 |
| ccaggatact | ccctcaaate | aagagtcttc | attactttta | gctattgcca | gattggaacc | 1020 |
| actttgattt | tgtctggggc | ctcgatgccc | ctcaacggat | gtacagtga | atcatagctt | 1080 |
| taatgaaggc | atattcctaa | atgcaatgca | tttacttttc | aattaaaagt | tgcttccaag | 1140 |
| cccataaggg | acttttagaaa | aaatagtaac | caacaatgag | gttgtcccc | agcaccctgg | 1200 |
| gggagatgca | cagtggagtc | tgttttccaa | gtcaattgtg | ttagtntat | ttatgttttag | 1260 |
| agacatcttt | gcctgggacc | atctacaggt | ccttataaac | aatgaggtag | attaggcaaa | 1320 |
| aagataaaca | agttgctact | ctatctggca | tttaagtcta | attaaattgt | aatttttagg | 1380 |
| gcataccatg | aagtatagaa | atgtctgaag | cttcaaagga | acagtgaat | tcctttaagg | 1440 |
| tcctatatgg | aaacctctgt | tgctatttta | tttatatgga | ttgctatggc | aatggacaga | 1500 |
| gtgtgggatt | aggaggaggg | cctgtaactt | ctttataaaa | gtttcttagc | tatcctgaag | 1560 |
| atgtatatag | atttttactt | ttttaggtat | tttcaacatc | agaaattcaa | aaaagtcctc | 1620 |
| aaagattctt | ccagagaagc | cctcttttct | tacaatctta | tccttggtta | tctgcgtaaa | 1680 |
| cggaaatctt | aaccataat | aggatacatg | tataaaatct | tccttattaa | agcagaaata | 1740 |
| aattgtacag | catcaatatc | attttataat | catagggagg | cttctttgtt | tagcatgtaa | 1800 |
| tgcccccttt | acaggctttt | tgttctttga | ggggtttgaa | cattccatga | aaaactgaca | 1860 |
| gataggaac | tgacaataaa | agattgagct | aaagatggaa | gcagaaagta | ctaggctaga | 1920 |
| tagtctctaa | atcttaagta | ttttcttctt | ccatcttaaa | agcaatgaga | agccaccaa | 1980 |
| atattttacc | taattggaac | ctgattgccc | cattttttgta | accaccactt | tggtgctac | 2040 |
| atagagaatg | gattagaaga | tgccaacaaa | agattctgag | caagactgta | aatctgatca | 2100 |
| agtgttctga | tgccagctga | tatccttctg | tgctaagaga | gatgatcctt | ggaaaatcca | 2160 |
| gagccagctc | cataataactt | tcctgctctg | ctggcaaatc | cacaagctgc | tgccccctgg | 2220 |
| agccattctt | ctctcaaaac | tagcattcat | caatttaattg | tatacgtatt | gatggggaat | 2280 |
| aatggtcact | atgaaaacca | tgtgataata | tggaaaaata | cccagatat | aatgttatgt | 2340 |
| gaagaggaga | aaatgaaact | ggtagaacta | tgtgattgca | aatatataca | aatattaaaa | 2400 |
| caatttatatg | actttataaa | atatttgtat | ataatgaaaa | ctgaagcaat | ataaaaaata | 2460 |
| aaattagttg | tgtcagggtg | gtaaaaaaa | aaaaaaaaa | aaaaaaaaa | aaaaaaa | 2517 |

<210> 25
 <211> 807
 <212> DNA
 <213> Homo sapiens

| | | | | | | |
|------------|------------|------------|------------|------------|------------|-----|
| <400> 25 | | | | | | |
| ccacgcgtcc | gcaaaatacc | tgagcccagg | taatttataa | agcaatgagg | tttatttggc | 60 |
| ttatgtttct | gcaggctgta | caagcttctg | gtaagggcct | caggaagctt | ccacacacgg | 120 |
| tggaagatga | aggggagcca | gaatgtgcag | attacatggg | gagagagtgg | aagcaagaga | 180 |
| gaggggcagg | aggggccagg | atcttttcaa | caatcagctc | atggatgagc | acagtggctc | 240 |
| atgcctgtaa | tcccagcact | ttgggagcac | aagatgggag | gatcacttca | gcccagaat | 300 |
| ttaattaaga | ccaaccagcc | tgggcaaaaa | agtgagactc | catctctaca | aaaaatcaaa | 360 |
| aaattaacca | gtcacggtgg | tgtgtgcctg | tggtccaaac | tacatgggag | actgagggtg | 420 |
| gaggattgct | tgagcccagg | aggtcaagac | tgcaagttag | tatgctcatg | ccactgcact | 480 |
| ccagcctcgg | caacagaatg | agacactgtc | ttaaaaaaa | gaaaagtga | tttataaaca | 540 |
| aaattttaaa | aaatcagctc | ttgtaaaaac | taagagttag | aactgactca | ttattgcaaa | 600 |
| gataacacta | acctattcat | aagggatctg | tccattatc | caaacacctc | ccaccaggcc | 660 |
| ccacctttaa | caatgggaat | caaattataa | aatgagactt | ggtagtcaa | caaatcatat | 720 |
| caaaccatag | cacctactct | cccacttctg | ttcaacatgg | gattgaagtt | ctttctagag | 780 |
| caattaggca | agaaaaaaa | aaaaaaa | | | | 807 |

<210> 26
 <211> 554
 <212> DNA
 <213> Homo sapiens

<400> 26
gaattccccg gtcgaccac gcgtccgaat ttcaaaaaca acgaaacctt cttttgcccc 60
ctccgcagca gtcgcctccg ggcttttattg caagttttacg gttccatata agtaaatccg 120
aaaaaaagtg tgtgtggggg ggtccacacc actaattatt atggcgagga agataaagaa 180
gacatggaca gaaggcggat ggctctgcgg cctggctccc gcagaccgac cgccttcttc 240
ttccattcga gatggctcgt accgaacctc cttgccttct tcctgggtct ctcgggggct 300
ggaccaatac atctgccgat gccctggccg aatggcaggc gacatcgggt cctggacccc 360
cacacgcagc tcagtaccca cgaggcccca ggccgctgga agcctgtagc tccgcggagg 420
atgaaagcct gccgcgaggt tctcctggag tggtagcct ctgtcggaag ggggcgcccc 480
cgtcttttta atgggtccta acacaccagt ggaataaatc tctaagattc cacaaaaaaa 540
aaaaaaaaaa aaaa 554

<210> 27
<211> 1319
<212> DNA
<213> Homo sapiens

<400> 27
ggcagcaggtt tcagggcaat tttatttctt ctgagagctt gtgggtcacct ctatgccagt 60
gattacaaaa ctaaattctt agtcttggct tttctcttaa atctataaat ctattccaca 120
tttctatcct cgtgatagac ttttttggga tggagtttct ccaactcaaa cctattttac 180
caccttttct tcaaagcttg ctctctttac taattttctca gtgtctgctg ttgggtgccac 240
tatttttctca gagataaact ttggagttct actagggtgc tcattttctct cacctgtcac 300
atcctgtcag tggccaatga tgtccattca ctgtgtacag cctctcctcc cattattttt 360
gccatcgtct tatttcaagc aattcttatt acttccctgg acttttggag tagccctcta 420
attggtttac agtctccaat tgtttttctt aatacatctt ataaaatact gatgactttt 480
cctaaaacca atcatgcgaa acctcagcct aaaattcttc atggagtttg attatctact 540
gaagaaaatg caaacttagc gtgacattcc agattttctt ggtccccgcc tacctttcta 600
attttatcta atctctacct ttaattcttg gtttatacct ttctgataac agtcactgtt 660
ttcagtagaa gctgaaaaga cactaacatt ttgttaggaa atgctaaatg ccttatatat 720
gtcacttaat tgcaagcata ggtaagatag gttttattcc catttttaaag gtgaagtaac 780
tgaggtttca gagagttcag gtttaatttg ccaagatcat acaacttgca agtagagcaa 840
tcaagggttg ttgattataa tatccacatg ctttctgtca cgttgtgtta attctttgtg 900
tacatgtcat tttccatttg cttaactttg gttaatctta aaagaaggat tgctgaatca 960
aagtatatat ccatttataa tgtgacacac attttcaaac tgccttctag aaaggttata 1020
ccaggctagg tgcagttgtc tcatgcctgt aatcctagca ctttggggagg ctgaggtggg 1080
cggacagctt gagctcagga gttcaagacc agcctgggca acatggtgaa accctgtctc 1140
tgtaaaaaat acaaaatttg ccggtcgtgg tggtagatgc ctatagtccc agagattgag 1200
gtgggaggat cgcttgagcc tgggagatga aggttgagc gaagctgaga ttgcaccact 1260
gcaccacagc ctggtgacag agtgaggccc tgtctcaaaa aaaaaaaaaa aaaaaaaaaa 1319

<210> 28
<211> 1487
<212> DNA
<213> Homo sapiens

<400> 28
ggcagcagcc ccgtccaggt tcatgttctt cttatttctc ctcacgtgtg agctggctgc 60
agaagttgct gcagaagttg agaaatcctc agatggctct ggtgctgccc aggaaccac 120
gtggctcaca gatgtccag ctgccatgga attcattgct gccactgagg tggctgtcat 180
aggcttcttc caggatttag aaataccagc agtgcccata ctccatagca tgggtgcaaaa 240
attcccaggc gtgtcatttg ggatcagcac tgattctgag gttctgacac actacaacat 300
cactgggaac accatctgcc tctttcgctt ggtagacaat gaacaactga atttagagga 360
cgaagacatt gaaagcattg atgccaccaa attagccgtt tcattgaga tcaacgcct 420
ccacatgggtg acagagtaca accctgtggc ctccccagag tatgaagaga acatgcacag 480
ataccagaag gcagccaagc tcttccaggg gaagattctc tttattctgg tggacagtgg 540
tatgaaagaa aatgggaagg tgatatcatt tttcaacta aaggagtctc aactgccagc 600
tttggcaatt taccagactc tagatgacga gtgggataca ctgcccacag cagaagtttc 660
cgtagagcat gtgcaaaaact tttgtgatgg attcctaagt ggaaaattgt tgaaagaaaa 720
tcgtgaatca gaaggaaaga ctccaaaggt ggaacctctga cttctccttg gaactacata 780
tggccaagta tctactttat gcaaagtaaa aaggcacaac tcaaattctc gagacactaa 840
acaacaggat cactaggcct gccaaaccaca cacacacgca cgtgcacaca cgcacgcacg 900
cgtgcacaca cacacgcaca cacacacaca cacacagagc ttcatctctt gtcttaaaat 960
ctcgttttct cttcttctct ctttttaaat tcatatcctc actccctatc caatttctct 1020
cttatcgtgc attcatactc tgtaagccca tctgtaacac acctagatca aggttttaag 1080
agactcactg tgatgcctct atgaaagaga ggcattccta gagaaagatt gttccaattt 1140

| | | | | | | |
|-------------|------------|------------|------------|------------|------------|------|
| gtcattttaat | atcaagtttg | tatactgcac | atgacttaca | cacaacatag | ttcctgctct | 1200 |
| tttaagggtta | cctaagggtt | gaaactctac | cttctttcat | aagcacatgt | ccgtctctga | 1260 |
| ctcaggatca | aaaaccaaag | gatggtttta | aacacctttg | tgaaattgtc | tttttgccag | 1320 |
| aagttaaagg | ctgtctccaa | gtccctgaac | tcagcagaaa | tagaccatgt | gaaaactcca | 1380 |
| tgcttggtta | gcattctcaa | ctccctatgt | aatcaacaa | cctgcataat | aaataaaagg | 1440 |
| caatcatgtt | ataggaaaaa | aaaaaaaaaa | aaaaaaaaaa | aaaaaaa | | 1487 |

<210> 29
 <211> 1889
 <212> DNA
 <213> Homo sapiens

| | | | | | | |
|-------------|-------------|-------------|------------|------------|-------------|------|
| <400> 29 | | | | | | |
| gaattccccg | gtcgacccac | gcgtccgatg | gggctgacgt | caactaccag | agcaaagaag | 60 |
| ggaaaagtcc | tctgcacatg | gctgcaatcc | atggccgttt | cacacgctcc | cagatccctca | 120 |
| tccagaatgg | cagcgagatt | gattgtgccc | acaaatttgg | gaacacgcca | ctgcatgtgg | 180 |
| ctgctcgata | tggacacgag | ctgctcatca | gcacctcat | gaccaatggc | gcagataccg | 240 |
| ccggcggtgg | catccatgac | atgttcccc | tgcacttagc | tggtctcttt | ggattctctg | 300 |
| actgttgctg | taagcttctt | tcctcaggtc | agttgtacag | cattgtgtct | tcactcagca | 360 |
| atgagcatgt | gctttcagct | gggtttgaca | tcaatacacc | tgacaacctt | ggccgtacct | 420 |
| gtcttcatgc | tgctgcttcc | ggaggggaatg | ttgaatgtct | taatttgctg | ttgagcagtg | 480 |
| gagctgactt | gaggaggagg | gacaaatttg | gcaggacccc | actgcactat | gcagctgcta | 540 |
| acggtagcta | ccagtgtgca | gtaacattgg | tgactgctgg | ggcaggtgtc | aacgaggccg | 600 |
| actgtaaagg | ctgctctccc | ctccactacg | ctgccgttc | tgacacttac | aggagagcgg | 660 |
| aacccatac | accttccagc | catgatgccg | aagaggacga | gccactgaag | gagtcccgcga | 720 |
| ggaaggaggc | cttcttctgt | ctggagtctt | tactggataa | cggtgcagac | ccctccctgc | 780 |
| gggacaggca | gggctacaca | gctgtgcact | atgcagccgc | ctatggcaac | agacagaacc | 840 |
| tcgaactgct | cttagaaatg | tcctttaact | gcctggagga | tgtggagagc | accattccag | 900 |
| tcagcccttt | gcacttagct | gcctacaacg | gtcactgtga | agccttgaag | acgctggcgg | 960 |
| agacgctggg | gaatctggac | gtaagggacc | acaagggccg | gaccgcactc | ttcctggcca | 1020 |
| cggagcggcg | ctctactgag | tgtgtggagg | tgcttacagc | ccacggcgcc | tctgccctca | 1080 |
| tcaaggagcg | caagcgcaag | tggacacccc | tgcacgtgct | tgctgcctct | ggccacactg | 1140 |
| actccctgca | cttgcctgatc | gacagtgggg | aacgagctga | catcacagat | gtcatggatg | 1200 |
| cctatggaca | gacccactg | atgctggcca | tcatgaatgg | ccatgtggac | tgtgtacatc | 1260 |
| tgctgctaga | gaaaggatcc | acagctgatg | ctgctgacct | ccggggccgc | actgccctcc | 1320 |
| accgcgggcg | agtgcactggc | tgtgaggact | gcctggctgc | cctgctggac | cacgagcgtc | 1380 |
| ttgtgctgtg | ccgagacttt | aaggggccgc | cgcccattca | cctggcctca | gcctgtggcc | 1440 |
| acactgcagt | actgcggaac | ctgctgcagg | ctgccctttc | cacagatccc | ctggatgccg | 1500 |
| gggtggatta | cagcggatac | tcgcccctgc | actgggcctc | ctacactgga | catgaagatt | 1560 |
| gtctggagtt | gttacttgaa | cacagcccgt | tttcgtacct | ggaaggaaac | cccttcaactc | 1620 |
| cttcaactgtg | cagtgaataa | taaccaagac | agcaccacag | agatgctact | gggagctctg | 1680 |
| ggtgccaagt | ttgtgaacag | ccgagatgcc | aaaggacgga | cccccccca | atcgagctgc | 1740 |
| caaatctctc | ggtttgcccc | gggatattat | agaaaattat | ttgtatgaat | aatgaaaata | 1800 |
| aaacacacct | cgtggcaaaa | aaaaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | 1860 |
| aaaaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | | | | 1889 |

<210> 30
 <211> 1192
 <212> DNA
 <213> Homo sapiens

| | | | | | | |
|------------|------------|------------|------------|------------|------------|-----|
| <400> 30 | | | | | | |
| ccacgcgtcc | ggtgaatata | tgtgtgagca | gatatggcta | taaagacctc | tagcttttgc | 60 |
| actttatgca | tatataatca | atcctttcta | gttcagtga | ttgaccccat | ccacaggtcg | 120 |
| attcatcttt | gtgttaaggg | gcaaataaaa | cggtatatta | tttctttgca | gtctcctctc | 180 |
| agtcattcat | caatgtggcc | agcttatcta | ctcccaatta | tgttggtgat | acatctccaa | 240 |
| gccatctgtc | atcagatcaa | aaagcagcaa | acagaggggc | agtcacagga | tggtctgaca | 300 |
| caccattgta | actttttgtt | agagatgatc | ccattttaga | aaagactggg | agaaattgga | 360 |
| gtgaaaggaa | ccctacagat | tagcccagtt | ctctcttatt | ttcagcttta | cagacaagaa | 420 |
| caattttaa | ctaaagaatt | tagtagattc | cttcagtgct | acaaagctgt | ttcatgaaag | 480 |
| aatcaagatt | ataacctgga | tattctgact | cctggcccag | tgctttttct | tactttgtag | 540 |
| ctacactttg | aagtaagatt | caaactgtta | tccactcaat | tgcccttatt | ctgaggatgt | 600 |
| agtgaaggaa | gaaaaagttt | tctggaattc | cgtaaattat | attttaagct | tatttcttca | 660 |
| aaattatttt | catatatcac | agatatatca | ttggaagata | taatttgcac | atatgttcat | 720 |
| tatcagtgtt | cctaattttg | tattacatgt | attctatttt | tttctgaatg | atagcatgaa | 780 |
| aagtgtcaaa | gtggtttgtc | cgctagcgtc | tgtctgcaga | actttcagga | tgactattaa | 840 |

| | | | | | | |
|------------|-------------|-------------|------------|------------|------------|------|
| ttcctctcag | atgtcatttt | tgagtgggtcc | aagcctgctg | ttttgaaccc | acagcagtgg | 900 |
| agatttgtat | tcttattttac | agttgtgtac | tataaagtgt | gtgttacata | ggtttttgtt | 960 |
| aataattatt | tgtaaattatt | atttagattt | gtatttagac | atgatttata | tctaatatag | 1020 |
| atacaaagtc | tgtgtctaaa | tattatttaa | agaagtgatt | tttcattctc | ttggattctt | 1080 |
| tccagtgtgg | tgccctttat | atgcctcaca | tagtctcctt | gttctcctac | taatattccc | 1140 |
| aagctccata | tgccaattaa | agaagaacaa | aaaaaaaaaa | aaaaaaaaaa | aa | 1192 |

<210> 31

<211> 1162

<212> DNA

<213> Homo sapiens

<400> 31

| | | | | | | |
|------------|-------------|------------|------------|-------------|-------------|------|
| tcgaccacg | cgctccggtt | ttcccttggc | caactccaca | ggtttgaacc | tggcattctg | 60 |
| gacaccagct | atgcctcctc | catttctcag | aaaacctttg | atcttgtgtg | tctttcttcc | 120 |
| tactgaaggg | aattgtgggg | gcagttcttt | ggccttcttg | ctgaactttg | ctggaaatag | 180 |
| cccacaattt | ttatcagagg | ttagaactgt | acattatcag | agagactgga | cactttatcc | 240 |
| cctagcaaag | tgggagaaga | ttttaccagc | tcattccact | ccaccctggc | cttccccac | 300 |
| cccccatccc | cagcagcatt | tccatggaaa | tccagatggg | cgtgtagtgt | tatggctctc | 360 |
| ttgtgataga | ctggccttca | tattggagag | ctagggagag | cccctgggag | ggagagagat | 420 |
| aaggcgctat | ctgccttcaa | tcagaacctt | cggtttaaaa | tcattctaaga | gtctatactt | 480 |
| gtgtgtacat | acgtatttat | ttttatttat | ttttatacaa | ttccattggc | atggctcttc | 540 |
| accgacccta | tgatttgcac | ttttattttc | tattgtgtgc | acacacaatg | cagtattaat | 600 |
| ggcaaccagg | taaattattga | tttatttttt | aaagcttttc | ttcagtgttt | tgtcaacctt | 660 |
| ttcaaagtgt | ctcccaaaaa | aggatgctga | agagcaattg | ctcccttaag | caacagattc | 720 |
| atattttacc | tgggttaata | caacaaaagg | cctgtataat | tgtcttttca | ttgttaacac | 780 |
| ccaaaatagc | atctatctag | acagtatccc | caaagaattt | ggaaaatctg | atgggtgtgag | 840 |
| cagcagccgt | tagtatcagg | gtttcccat | cttggacagt | ccgaggctgt | gacctgttag | 900 |
| ataattagat | tatacttgaa | ctggaccaga | gtttgttttt | tgaatttatg | agaaaaacca | 960 |
| aaacactaag | ttaagtttga | acttgtaaag | tattgaaatt | tgttgagtgt | cctataaatt | 1020 |
| gtcactactt | ttcctgatct | gtataactga | ctgcaaagtg | tttgttttta | caaaagagaa | 1080 |
| aagaaaagat | ttttaataaa | gagaatttga | aagctgaaaa | aaaaaaaaaa | aaaaaaaaaa | 1140 |
| aaaaaaaaaa | aaaaaaaaaa | aa | | | | 1162 |

<210> 32

<211> 2799

<212> DNA

<213> Homo sapiens

<400> 32

| | | | | | | |
|------------|-------------|-------------|-------------|-------------|-------------|------|
| tcgaccacg | cgctccggaga | agactggagc | tccgaggagc | tgcattctgcg | gcaacctgtg | 60 |
| tgctgacgct | acgtgcctcc | tggctccgac | gtagctcgca | gctccccagt | ctcactccat | 120 |
| tccttcccca | cctggcgcg | acctgctcaa | gaccagggtc | ctgccaagcg | ctaggagggc | 180 |
| gcgtgccagg | ggcgctaggg | aactgcggag | cgcgcgcgcc | atggggccgc | cgcttggggc | 240 |
| cggggtctcc | tgccgcggtg | gctgcggctt | ttccagattg | ctggcatggg | gcttctctgt | 300 |
| ggccctgagt | ccgcaggcac | ccggttcccg | gggggctgaa | gcagtgtgga | ccgcgtacct | 360 |
| caacgtgtct | tggcgggttc | cgcacacggg | agtgaacctg | acgggtgtgg | agctgagcga | 420 |
| ggagggcgtg | tacgcagcgt | actcgcgctg | ggagcctgtg | gctgggggtcc | tggtagccgc | 480 |
| cgacgggccc | ggggcgctta | acgcctgtaa | ccgcacacg | aatttcacgg | tgcccacggg | 540 |
| ttgggggaag | accgtgcaag | tctcttgggt | ggccctcatc | caacgcggcg | ggggctgcac | 600 |
| cttcgcagac | aagatccatc | tggcttatga | gagaggggcg | tctggagccg | tcattctttaa | 660 |
| cttccccggg | accgcgaatg | aggctcatccc | catgtctcac | ccgggtgcag | tagacattgt | 720 |
| tgaatcatg | atcggcaatc | tgaaggcacc | aaaaattctg | caatctattc | aaagaggcat | 780 |
| acaagtgaca | atggtcatag | aagttaggaa | aaaacattgg | ccttgggtga | atcactattc | 840 |
| aatttttttc | gtttctgtgt | ccttttttat | tattacggcg | gcaactgtgg | gctattttat | 900 |
| cttttattct | gctcgaaggc | tacggaatgc | aagagctcaa | agcaggaagc | agaggcaatt | 960 |
| aaaggcagat | gctaaaaaag | ctatttgaag | gcttcaacta | cgcacactga | aacaaggaga | 1020 |
| caaggaaatt | ggccctgatg | gagatagttg | tgtgtgtgtg | attgaattgt | ataaaccaaa | 1080 |
| tgatttggta | cgcactctta | cgtgcaacca | tattttccat | aagacatgtg | ttgaccatgt | 1140 |
| gctgttagaa | cacaggactt | gccccatgtg | caaatgtgac | atactcaaag | ctttgggaat | 1200 |
| tgagggtgat | gttgaagatg | gatcagtgtc | tttacaagtc | cctgtatcca | atgaaatata | 1260 |
| taatagtgcc | tcctcccatg | aagaggataa | tcgcagcgag | accgcatcat | ctggatatgc | 1320 |
| ttcagtagag | ggaacagatg | aaccgcctct | ggagggaacac | gtgcagtcaa | caaataagaa | 1380 |
| tctacagctg | gtaaacatg | aagcaaatcc | tgtggcagtg | gatgttattc | ctcatgttga | 1440 |
| caacccaacc | tttgaagaag | acgaaactcc | taatcaagag | actgctgttc | gagaaattaa | 1500 |
| atcttaaaaa | ctgtgttaaat | agaaaacttg | aaccattagt | aataacagaa | ctgccaatca | 1560 |

| | | | | | | |
|-------------|-------------|-------------|------------|-------------|------------|------|
| gggcctagtt | tctattaata | aattggataa | atttaataaa | ataagagtga | tactgaaagt | 1620 |
| gctcagatga | ctaataattat | gctatagtta | aatggcctaa | aataatttaac | ctgttaactt | 1680 |
| ttttccacaa | actcattata | atattttttca | taggcaagtt | tcctctcagt | agtataaca | 1740 |
| acatttttag | acattcaaaa | ctgtcttcaa | gaagtcacgt | ttttcattta | taacaatttt | 1800 |
| ctataaaaa | catgttgctt | ttaaaatgtg | gagtagctgt | aatcacttta | ttttatgata | 1860 |
| gtatcttaat | gaaaaatact | acttcttttag | cttgggctac | atgtgtcagg | gtttttctcc | 1920 |
| aggtgcttat | attgatctgg | aattgtaatg | taaaaagcaa | tgcaaactta | ggcgagtact | 1980 |
| tcttgaaatg | tctattttaag | ctgctttaag | ttaatagaaa | agattaaagc | aaaatattca | 2040 |
| tttttacttt | ttcttatttt | taaaattagg | ctgaatgtac | ttcatgtgat | ttgtcaacca | 2100 |
| tagtttatca | gagattatgg | acttaattga | ttggtatatt | agtgcacatca | acttgacaca | 2160 |
| agattagaca | aaaaattcct | tacaaaaata | ctgtgtaact | atttctcaaa | cttgtgggat | 2220 |
| ttttcaaaaag | ctcagtatat | gaatcatcat | actgtttgaa | attgctaattg | acagagtaag | 2280 |
| taacactaat | attggtcatt | gatcttcgtt | catgaattag | tctacagaaa | aaaaatgttc | 2340 |
| tgtaaaatta | gtctgttgaa | aatgttttcc | aaacaatgtt | actttgaaaa | ttgagtttat | 2400 |
| gtttgacctt | aatgggctaa | aattacatta | gataaactaa | aattctgtcc | gtgtaactat | 2460 |
| aaattttgtg | aatgcatttt | cctgggtgtt | gaaaaagaag | ggggggagaa | ttccagggtc | 2520 |
| cttaatatata | agtttgaagc | ttcatccacc | aaagttaaat | agagctattt | aaaaatgcac | 2580 |
| tttatttgta | ctctgttggtg | cttttgtttt | agaattttgt | tcaaattata | gcagaattta | 2640 |
| ggcaaaaaata | aaacagacat | gtatttttgt | ttgctgaatg | gatgaaacca | ttgcattctt | 2700 |
| gtacactgat | ttgaaatgct | gtaaatatgt | cccaatttgt | attgattctc | tttaaatata | 2760 |
| aaatgtaaat | aaaatattcc | aataaaaaaa | aaaaaaaaa | | | 2799 |

<210> 33
 <211> 1656
 <212> DNA
 <213> Homo sapiens

| | | | | | | |
|-------------|-------------|-------------|-------------|-------------|------------|------|
| <400> 33 | | | | | | |
| ccacgcgtcc | ggagtggaaat | tcccaagggtg | ctggagggttg | aaaggcattg | agaatctaaa | 60 |
| acgcttttgca | gacagcaaga | ccctctgtgt | aagttaagaa | tgctcactca | gtcccagcag | 120 |
| gtactcagag | ggatcctttt | atctctccag | aacattctgc | aggtgagctg | gggaagccca | 180 |
| ctggccctgg | cctcaccctcc | gagcccagagc | cttcagcctg | ggaatgggtct | ggcctcttcc | 240 |
| ttgctggctc | tccagcctgg | cctcgcagga | ccctgggctgg | gaccccagga | accctcacc | 300 |
| gctatgtgct | tccccaagaa | gcgctccctg | tggcctaatt | tgagaaaaca | atgggcctca | 360 |
| atccatatta | atgaccctag | agggaccctt | tgtctcgggt | gcacaggctg | taatcagcg | 420 |
| ggctccgggg | gctctggcct | aatttggagg | gacagggttt | atcatcacc | ttgattcggg | 480 |
| tgacccaatc | tgacaggccc | acgacccctt | gtatgcgggg | tccacgtcag | agatgggctt | 540 |
| cctcccagcg | gccaccccca | gcgggctggg | gagagggaag | ggggagggtg | tggccatggg | 600 |
| ggaagttcgg | ggtgaagaag | gggtcacagc | cagaccccca | cttggatggg | cctgtgatcg | 660 |
| ggttctcggg | aggagcagga | tattgattag | atcagtgaat | ggtgtggagg | cagctctccc | 720 |
| caggcacgtg | ctcccgaaca | cccaccagca | agcgtctgtt | gcctgccggg | gccagggctg | 780 |
| ggtggggact | ctgggacagg | ccggctgcct | aggaggggcc | aggcaggagc | caaggggctg | 840 |
| gctccaggga | ctgccaggag | ggccccaggg | aaggggagcc | gggaagcgtt | ttggctgcct | 900 |
| ccggcgtaga | gtcgtggaaa | cgtgtttgca | ggttagggcc | gtggcatcct | cgttgacca | 960 |
| tttgagcgcc | tatgggggtg | cagatacatg | acaaaggggc | acctcattta | atgcttccct | 1020 |
| caaccttccc | aggccccgat | ccccatgttc | tgggtcagga | ggcccatctg | aggtcaaggg | 1080 |
| gtgggcgaag | gctgacgaga | caaaccagg | gactagtctc | tgagtcccaa | aacctgtcct | 1140 |
| caccacccca | gggttcccc | gcacgctctc | cagggtgtgc | ggtgcgtggc | tgctgggttt | 1200 |
| gggtgcatta | gagcctgagg | caagggtctg | agtctgaatt | ctcgctacgg | accaaattgt | 1260 |
| tgctctctcc | ctaaatacat | atgttgaagc | cttaactccc | aatgtgatgg | cattaggaga | 1320 |
| ggggacctgt | ggaatgtagt | tgagtctctg | gggtgcggcc | ccgtgatgaa | attagtggcc | 1380 |
| tgataagaag | aggcccagag | aaccggctct | gtctctgctc | tctgtcgcac | gaggacccca | 1440 |
| caagaagacg | gccacctgca | aacagccatt | gaatctgcca | gtgacttggg | cgtggagttc | 1500 |
| cagcctccag | aactgtgaga | aataaatgtt | tgcgatttaa | accgcaaaaa | aaaaaaaaaa | 1560 |
| aaaaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | 1620 |
| aaaaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | aaaaaa | | | 1656 |

<210> 34
 <211> 2051
 <212> DNA
 <213> Homo sapiens

| | | | | | | |
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| <400> 34 | | | | | | |
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| ggtggcaggc | ccctgtaatg | ccagctactc | aggaggctga | ggcaggagaa | ttgtttgtat | 120 |
| ccgggaggcg | gagtttgag | tgagccgaga | tcgtgccact | gcactccagc | ctaggcaaca | 180 |

| | | | | | | |
|-------------|-------------|-------------|-------------|-------------|------------|------|
| aaccaagact | ccatctcaaa | aaataaaaaat | aaaaaaagca | ggtgatggga | tgacatggag | 240 |
| tttttgtttt | gctttgtttt | gttttgtttt | gttttttgc | gcttccctga | taggctatat | 300 |
| actgctccct | tcagcctctc | cccgaaccca | caggcgccca | aacaatgagg | ccagggttgg | 360 |
| aacccttggc | cagctagatg | atgagctgaa | ggggaggcaa | ccttttagcca | gcagacttga | 420 |
| gacatctcag | tgtactcagg | gtctgctggc | tagcaggccc | agtggggtct | ccaaagccct | 480 |
| tctgtatcct | taattggctc | taaaccctgg | ttgaagatcc | ccccagttgt | gtttacttaa | 540 |
| gccagaaggc | tgggcaatct | ctatatacct | tctccatcga | tcatacctatg | attgttttgt | 600 |
| tagagaatta | ttattgttca | gggtaccaga | tcttagtttc | attccacaga | taataagtcc | 660 |
| ggctccaggc | tgggcatggg | ggctcacacc | tgtaatccct | gcactttgag | aggccaagg | 720 |
| gagtggatca | cttgaggcca | ggagcttgag | accagcctgg | ccaacatggg | gaaaacccat | 780 |
| ctctactaaa | aatacaaaa | tttgcagggt | gtgggtgtgc | gggaagtcag | ggaccccaaa | 840 |
| cggagggaac | gtctgaagcc | atggcagaac | gtggattgtg | aagacttcat | ggacatttat | 900 |
| tagttcccca | aattaatact | tttataattt | cctatacctg | tctttactgc | aatcttggaa | 960 |
| cataaaaattg | tgaagatttc | atggacactt | accacttccc | caatcaatac | ccttgtgatt | 1020 |
| tcctatgcct | gtcttacttt | actttcttaa | tcctgtcagc | tgaggaggat | gtatgtcgcc | 1080 |
| tcaggactct | gtgataattg | cgtaacttgc | acaaattgta | cagcatgtgt | gtttgaacaa | 1140 |
| tatgaaatgt | gggcaccttg | aaaaaagaac | aggataacag | caattgttca | gggaataaga | 1200 |
| gagataacct | taaactctga | ccaccggtga | gccgggtgga | gcagagccat | atttctcttc | 1260 |
| tttcaaaagc | aaatgggaga | aatatcgctg | aattcttttt | ctcagcaagg | aacatccctg | 1320 |
| agaaagagaa | tgcacccctg | aggggtgggtc | tataaatggc | ccccttgggt | gtggccgtct | 1380 |
| tctatgggtc | agactgtagg | gatgaaataa | accctagtct | cccatagtgc | tcccaggctt | 1440 |
| attaggaaga | gaaaattccc | gcctaataaa | ttttgggtcag | accggttgct | ctcaaaaccc | 1500 |
| tgtctcctga | taagatgtta | ccaataacaa | tgggtgccga | aacttcatta | gcaattttta | 1560 |
| tttcgccttg | gtcctctggg | cctgtgatct | cgccctgcct | ccatttgcct | tgtgatattc | 1620 |
| tattaccttg | tgaagtacgt | gatctttgtg | acccacaccc | tattcgtaca | ctccgtcccc | 1680 |
| ttttgaaagt | ccctaataaa | accttaccgg | ttttgcggct | tgtggggcca | tcacggagcc | 1740 |
| taccgacatg | tgatgtctcc | cccggatgcc | cagctttaaa | atttctctct | tttgtactct | 1800 |
| gtccctttat | ttatcaaact | ggccgacgct | tagggaaaaa | agaaaagaac | ccacatgact | 1860 |
| atcggggcag | gttccccaat | agtgtgggtg | caggcgccctg | taatccaagc | tgtttgggag | 1920 |
| gctgaggcag | gaaaataaact | tgatcccgag | aggcagaggt | tgcagtgagc | caagatcgcg | 1980 |
| ccactgcact | ccagcctggg | caacagaggg | agaccctgtc | tcaaaataca | taagtaaaaa | 2040 |
| aaaaaaaaaa | a | | | | | 2051 |

<210> 35
 <211> 2053
 <212> DNA
 <213> Homo sapiens

| | | | | | | |
|-------------|------------|------------|-------------|------------|------------|------|
| <400> 35 | | | | | | |
| ccacgcgtcc | gaagaaacct | gccacagatg | gaatggcagt | tgggaaaacc | ctcattcctc | 60 |
| ctcagcctcc | tgatgttgct | agtcctcgag | tggaaagctc | tatgcggagt | acgtctgggt | 120 |
| cacctaggcc | tgcagggtgc | aaacccaagt | ctgaaatcca | cgtgtctatg | gccactccgg | 180 |
| tcactgtgtc | catggagact | gtatccaatc | aaaataatga | tcagcctacc | attgccgtcc | 240 |
| ctccaactgc | ccagcagccc | ccaccgacca | ttccaactat | gattgcagca | gccagtcccc | 300 |
| cgtcacaacc | agccgttgcc | ctttcaacca | ttcctggagc | gggtcccatc | actccaccca | 360 |
| tcaccaccat | tgcagctgca | ccacctccat | cagtcactgt | gggtggcagt | ctttcctccg | 420 |
| tcttggggcc | tcccgttctc | gaaattaaag | tgaagaaga | agtagaacca | atggatatca | 480 |
| tgaggccagt | ttctgcagtt | ctccactggg | ctaccaaac | tgtgtctcca | tctcttgc | 540 |
| tgttggcaaa | caacttgtcc | atgcctacaa | gtgacctacc | acctgggtgc | tccccaagg | 600 |
| aaaagcctcg | aaagcaacag | catgtgatct | caacagaaga | aggtgacatg | atggagacaa | 660 |
| acagcactga | tgatgagaag | tccactgcca | agagtcttct | ggtgaaggct | gagaagcgca | 720 |
| agtctcctcc | caaggagtat | attgatgagg | aagggtgtgag | atatgtccca | gtgcgtccaa | 780 |
| gaccccccat | tactttgctt | cgtcactatc | ggaacccctg | gaaagctgct | taccaccact | 840 |
| ttcagaggta | cagtgcagtc | cgggtcaaag | aggagaagaa | agctatgctg | caggaaatag | 900 |
| ctaatacagaa | aggagtatcc | tgtcgtgtct | aaggctggaa | agtcacacct | tgtgtgtccc | 960 |
| agttactaca | gctgacgaat | ctagaacatg | atgtctatga | aagacttact | aacctgcagg | 1020 |
| aagggattat | cccaaagaaa | aaagcagcaa | cagatgatga | tctccaccga | ataaacgaac | 1080 |
| tgatacaggg | aaatatgcag | aggtgtaaac | ttgtgatgga | tcaaatcagt | gaagccagag | 1140 |
| actccatgct | taaggtttta | gatcataaag | accgtgtcct | gaagctgctt | aacaagaacg | 1200 |
| ggactgtcaa | aaaagtgtcc | aaattgaagc | gaaaggaaaa | agtctagacc | cagaacaatc | 1260 |
| aggagattgg | aagcaaat | atgaagaatg | atgggtggggg | tggggggagg | gttttgggtt | 1320 |
| tttccaaagt | ggaacattga | aataaaggaa | gtgttcttta | gttcccgtgt | gaaagcagag | 1380 |
| gaacccatga | catccaaggg | cgtgaaagga | tcagagctga | ctggacatag | tgagctgcct | 1440 |
| tcttgcgttc | gggtgcaccc | ctgttaaac | tgatctgtgt | cataagtga | tccgatgca | 1500 |
| tcagtgtcca | ccagttggaa | gcaatgacaa | ggatggctgg | ctggtgtttt | tcagccttcc | 1560 |
| ggtttataga | ctgtatttat | ctagtggatt | cctgcaggcc | ccatactgag | cctggactga | 1620 |

| | | | | | | |
|-------------|------------|------------|------------|------------|------------|------|
| aagtatccac | tcggaccatc | tgttatctct | ctacactgaa | aataaaacct | cttccaccca | 1680 |
| ccccattcgg | ttcttctgcc | tgaccttcaa | atgcccattg | tggcctttta | cagcagtgcc | 1740 |
| acggcaccaa | gcgagctgcc | acatctcaca | ctctaaagg | tttgaactat | tagttcttgt | 1800 |
| catttttttaa | aaaaaaccat | tcccaagtga | aattgttata | tcgtctgtct | tgctgtgtct | 1860 |
| agaactgggt | ttttgtggag | gttcagagca | ggcaacacca | taagttgctc | tcagatcctt | 1920 |
| gttctgaagt | acattcttgg | ttatctgtac | ttctgtagct | gggtgatgc | tgtaattgt | 1980 |
| atgtaccaca | catctccaga | cgtaataaaa | ggactcaaag | aggtttttgt | aaaaaaaaa | 2040 |
| aaaaaaaaa | agg | | | | | 2053 |

<210> 36

<211> 576

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (538)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (565)

<223> n equals a,t,g, or c

<400> 36

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| gcaacatagt | gccctgactc | tactaaaaaa | aaaaaatctg | tctccttggt | tcagtcctca | 60 |
| cggctttttgc | agtagtcga | ggcttcttca | tctctcacct | acacattgca | atgcctttgc | 120 |
| ctcctaaatg | gcctccctta | ctcactgctc | tcctatgcc | tcttctatct | acctcatcac | 180 |
| cacttcta | tatccttcca | aatcacagg | ctgatcatcc | actcacagac | ctatcgkggc | 240 |
| tttccattgc | ctacaaaaat | gaaaaccaaa | ccacagaact | tagcatgaca | gtaaaagccc | 300 |
| tgcatttagc | ctccatctac | tgtatccttc | atgcatctta | aactcttgct | tattccagat | 360 |
| aacttgccct | tgcattgaa | caccctcact | ttgagtgtct | ctttgagcat | accttccctc | 420 |
| ctttcatcca | caccatctta | caaaaatcat | cctttttgag | cagctcaa | atcatttctt | 480 |
| ccaggaaatt | tyccacgact | ttcttycaat | ccaaattaat | taatctctct | tttctccnag | 540 |
| gtcatacagc | tctatctatc | tatcnatcta | tctatc | | | 576 |

<210> 37

<211> 1290

<212> DNA

<213> Homo sapiens

<400> 37

| | | | | | | |
|-------------|------------|------------|------------|-------------|-------------|------|
| gggtcgaccc | acgcgtccga | tttctgacct | cgtggggcgt | gtgggtctccg | gatggctggg | 60 |
| agatgcagtc | ccagggcctg | tgacacgact | cctgatgctc | tggaccacct | tgactggggg | 120 |
| gtcactagcc | ctgttccctg | tagctcaggc | tcccacagcc | ctgggtggctc | tggtgtgggc | 180 |
| ctacggcttc | acatcagggg | ctctggcccc | actggccttc | tccgttctgc | ctgaactaat | 240 |
| agggactaga | aggatttact | gtggcctggg | actgttgag | atgatagaga | gcacggggg | 300 |
| gctgctgggg | cctctctctc | caggctacct | ccgggatgtg | acaggcaact | acacggcttc | 360 |
| ttttgtgggtg | gctggggcct | tccttctttc | agggagtggc | attctctctca | ccctgccccca | 420 |
| cttcttctgc | ttctcaacta | ctacctccgg | gccccaggac | cttgtaacag | aagcactaga | 480 |
| tactaaagtt | cccctaccca | aggaggggct | ggaagaggac | tgaactccac | agagtcaggc | 540 |
| ccagaaagcc | aagcttgaca | gctcagggtc | tctcttgccc | gtcttgggtc | ccacagaacc | 600 |
| cagtgcctta | agattcttga | tctgcctccc | cctagagcag | gcctggggct | cctgcaatgt | 660 |
| gtgtgccaac | cctttgtatt | ttgttgagga | ctcttatttc | tccgttactc | tcctaaccctt | 720 |
| ttcttctttt | ttctttttcc | cgagacggag | tcttgctctg | ttgcccaggc | tgagtgagc | 780 |
| tgatgtgac | tcggctcact | gcggcctccg | cttcccgggt | tcgggcgatt | ctcctgcctc | 840 |
| agcctcccaa | gtagctggga | ttacaggcgg | gagccaccac | acccggctat | tttttttttt | 900 |
| ttttttttga | tttttggtag | agacgggggt | tcgccatggt | ggccgggatg | gtctcgaact | 960 |
| cctgaccttg | tgatccaccc | cccccccccc | ctcggccttc | caaagtgctg | ggattgcagg | 1020 |
| cgtgagccac | cacaccagc | ctcccctaac | cttttctaaa | ggaccaggga | gttttgagg | 1080 |
| atccgggagt | tcctgcttca | ctgagctgtg | aatcaactgt | gaaaatcaaa | ggccaagaga | 1140 |
| cttatcatgc | tttatataac | atctctagt | ttgcctcctg | agtttcttct | ctgaagacac | 1200 |
| atgtttggga | aacaaaactg | tccctttgag | ataaaatcaa | ataagaaaat | tggaataata | 1260 |
| tcacaacctc | aaaaaaaaaa | aaaaaaaaaa | | | | 1290 |

<210> 38

<211> 1322
 <212> DNA
 <213> Homo sapiens

<400> 38
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 atttgtttta taccagtggc tgggatgggt gaattggggg tatttctaca attattctta 180
 gacgattact aaactgttaa gaaatgcccc atatcatttt tgtatctagg aaagaaaaaa 240
 atcagtttca tactgttgtc atctgtcaga aatgctcatt ttattttgaa ttaaagtgtg 300
 cttttgaagt acctagttac cttgaattcc tggtgaccac atgtttttat ctggaaaacc 360
 tggagaaagt tatctgtccc atctccccctg cttgtttttt tttttttttt tttttgggtg 420
 gagctgctgt ttagatgatg cttttactat gcaggagaga gtttttggtta aggatatatt 480
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 ttcattttac acttgtgagt ttatcattga ctttaagagg tagaaatgaa aaatgaaaat 660
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 aacccaagaa gataatttaa atctatactg cttattgggtc aatatatttg gttctagtag 1080
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 tgttgattta tagctgtttg agatgataaa agtgaagcaa agcctgttaa atcattggaa 1200
 gacttggaaa attattttta ataaacaatt acatgtaatt aaaaaaaaaa aaaaaaaaaa 1260
 aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1320
 gg 1322

<210> 39
 <211> 1877
 <212> DNA
 <213> Homo sapiens

<400> 39
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 agcctccttt atccttttga ccacaagatt ctctaggcac atcttatata tttccggccc 180
 cagtccctaga atcagccact tctccaagga gccctgattc tttttattag agaatggtat 240
 tagaaaccaa gttctaggca ttgggtgtgc ttgctactgg gatgttgtgg cttgtaggac 300
 ctttcagctg actgagcaag ggatgtacat gtatgtatac taaactaagt tttcttgtat 360
 gcagctactc gtatctatat taagctaaac atgagttgat gtttccaatt ctatccatta 420
 ccactctatc cattctagcc ttcttccttt gggtatctgt cacctctcac ttctacagac 480
 agaaaactgg ctttcatcat tcaccatctt tttacttaat tgttcaaate tgggatacat 540
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 tagtaattga aagcaggctt gttcagttgg gtttccagct caccctgctt cactacttaa 1260
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 ctctgcccct ctaaaaatc aaaaactagc caggcgtggt ggcagccacc tgtaatccca 1740
 gctacttggg gagccaaggc aggagaatca cttgaaccca ggaggcgcag gttgcagtga 1800
 gccgagaccg tgccattgca cgcagcctg ggggacaaga gcgagacttc gtctaaaaaa 1860

aaaaaaaaaa aaaaaaac

1877

<210> 40
 <211> 2559
 <212> DNA
 <213> Homo sapiens

<400> 40

| | | | | | | |
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| gaattcggca | cgaggggctt | gtaaattgtgt | gtgagtttct | gagtgtaggt | gccgaataaa | 60 |
| tgtttattga | tgatgcctac | ctatgcaatc | tgcattgtgc | ttgtatttct | attgcttgtg | 120 |
| cattttgcac | tcataaacac | aaacacacac | acacacacac | acacacacac | acacacaggc | 180 |
| ttgcttccag | agccatacat | gctctatttt | cagtttctga | gtgtcctaag | aggttatatc | 240 |
| ctgtctagat | ggacggaccg | agagtacact | tggatttcta | ccaagatata | ttctcctaata | 300 |
| tcaccagaac | ccccgccttc | ctgcccattc | cctacacaga | gcattctcac | ccatgcagtg | 360 |
| caggggaagca | catttctcaa | agctcagctg | cccacctctg | agcaggtgca | aatccaccca | 420 |
| ctgcattcct | ccatccacct | ttctccccct | tgaatttctg | tctcctccta | aatgggtctct | 480 |
| tttccccctg | cctcctcctc | cttcgttttc | cttctccaga | gaggcagagg | ttaggtgtgc | 540 |
| ttgaccagga | ttcaccaagt | gcagacatca | aaacagcaaa | gggatgtgga | caccatctcc | 600 |
| agcctctcgt | ttcatggact | ggctaagggt | cagggatgct | gaaggatttc | tcccatgtgc | 660 |
| ccaaggtagt | tcacagaaga | gcctgtctca | gagcgtgtgt | tttcccagcc | tttcccacaa | 720 |
| cctggccccc | ggtggaggaa | gcggttcccc | tccaccgacc | cctgcctccc | acatcagagg | 780 |
| tactgcaccc | aatgagtgcg | gccaaccaag | accaccaggg | gatgaaatga | gtcacatcga | 840 |
| ctgtctctag | gatggaaact | tggtagggat | tctgtttcct | gtgagcagga | agaacgcgag | 900 |
| atgagacaca | ggaggaccga | tctgtctgct | ctcaggcctc | tcatatgact | tcacagagga | 960 |
| caacttttgg | ccctccccgc | ccagctctgg | caggtgcatg | tcagtggact | ctgtccaaca | 1020 |
| ggcagagtcc | acggaaagga | aggacaagat | gatgtaagca | tgagatccca | gatgctggcc | 1080 |
| ctgggagggg | ttttaggggac | catctcctca | ttcagtgtct | ttgcattaca | cagaaactgg | 1140 |
| gcacatagag | gctccaggac | tggccaaggc | caccgggacc | ggtcccaggc | tttgactctc | 1200 |
| caggggtgct | tcccattttac | aaacctctgc | cgtccatttc | tttttggagt | gagtcctggt | 1260 |
| ggcactccca | taggaacagc | gtgtggggag | gcctagggtg | ggcctggcct | cagatgagga | 1320 |
| caccatccaa | gtgaccgggc | cgctgcattc | ctgctctttg | tgccacaccc | caagtcctct | 1380 |
| tgttccccgg | agatggagca | gatgacagag | gcgcacggag | gaagcggggc | tggggacaca | 1440 |
| cgggtgtgcc | agctcttttc | tccacctggg | tgcacctcca | caaactctact | gctccggggg | 1500 |
| tcccgcgcgc | gtccccaggc | agccaggagg | tgcgcgggtc | ggcggaggaag | gggctgcggc | 1560 |
| cgcgcgggtt | ctttctccaa | gacaggcgcg | ccctctgctg | ctagaactag | gaagcgcgcg | 1620 |
| cctggcccg | ctcagaccgc | gagcttggaa | cccgcagccg | cccgcaccct | ccagagaaac | 1680 |
| cggcttagaa | aagcctgccg | ccgcgaaagc | aaccagaggc | cctcccgcct | ccgggggtgt | 1740 |
| ctgaggactc | agacaggagg | gaatagaacc | tgggaggaga | aggaagagga | gctacctgaa | 1800 |
| ctctgtgagg | aaagggaggg | gacctttgca | tttgggattt | aggacaaaat | ccttgcatct | 1860 |
| gggatttagg | ctccttcccc | atcctttgtc | ctctccacga | agctcctctc | accccaacca | 1920 |
| ccaaactgtg | cccatgaagt | gaatggccca | ataaggagcc | tgtgggagcc | acagtatctg | 1980 |
| gagattttac | ctggccattc | cttgagccct | gggaaaagtt | ttaaaatgtt | cacttttgca | 2040 |
| acttcgagcc | tgggtcaaa | catgggtgtc | ccgcaggaag | agtagaggac | tgggaatgag | 2100 |
| gcctcctgga | atctgggttc | atttcaacca | ctcttttccc | ctgtgctaag | tcccggtgtc | 2160 |
| tctctgtggc | tcagtttctc | gacctattta | ttacatgggc | ctctcatgtc | ccggaaaatt | 2220 |
| cactgaggta | ccaggatatg | tacagcacta | gcaagccgtc | gtgccactgc | cctgctctgg | 2280 |
| ctgggtgtgc | ttttctctga | aatgggcagt | ggtaagagga | gggtggagac | agagcctccg | 2340 |
| gccaatctcc | ctgctcctcg | ccccctctgg | gactcccact | gcgcagtgtt | tccctcatat | 2400 |
| ctctggacaa | tcccacagac | tccttctctc | aggcaaggca | tccccaagga | agtgcataata | 2460 |
| aaaatgctgt | tgggtggtgga | ggcaacatat | tcagtgaata | tccaccaagg | ttactggctg | 2520 |
| aggctggagc | aggatggggg | tgaggggaat | actgctcga | | | 2559 |

<210> 41
 <211> 2116
 <212> DNA
 <213> Homo sapiens

<400> 41

| | | | | | | |
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| tcgacccacg | cgtccggcgg | agcttgcagt | gagcctagat | agagccactg | cactccagcc | 60 |
| tggggcacag | agggagactc | tgtctcaaaa | aaaaagaaaa | aaaaaagaaa | aagagaaatc | 120 |
| tatgacatca | cttgccaggc | tcccatgttc | ttacctctgc | ctgccttgcc | agctctcctc | 180 |
| ctgtctgtgc | ttctctcagc | ccatctctgc | acttcttccc | agtccttcaa | cacctgtgct | 240 |
| tctctctgcc | cccaggcctt | ccagccaggg | ggccccaggc | accagaagtg | aattccccct | 300 |
| aacccccctt | tgtctgccct | ccttcccacg | tgaatccttc | cttgattcct | ttcatctggt | 360 |
| cagctcccat | tagtatgtct | tctttgcagc | ctgccccttc | tcttttcagt | gcgtgatcac | 420 |
| aactgtatta | ggcaatcacc | tgtctaattg | ctgccttctt | aattagaact | tcaaattcac | 480 |

| | | | | | | |
|-------------|------------|------------|-------------|-------------|-------------|------|
| gtgggcataa | catcggtctg | ccttatttct | tgtggtatcc | tggatgtcga | acataacacc | 540 |
| tggcacctgg | tgggcaatga | ttaaatat | tgtggaaaga | atgggcaaaa | taaaagagta | 600 |
| aaaaaaaaatg | agtgcagat | acagtgaagt | gatgtggcaa | tattgctaac | ttttaaaaaat | 660 |
| attgtcaaag | agatactgag | ttcgaggaag | aggaagatag | aaattatgct | ggaaatgctg | 720 |
| gagagataag | gagtaatgag | atgactttct | gaggtgagct | catgcctgta | atcctagcac | 780 |
| tttgggaggg | caaggcagat | ggatcatgag | gtcaggagtt | caagaccagc | ctgaccaaca | 840 |
| tggtgaagct | ccttctctat | taaaaataca | aaaattatct | gggtatgggtg | gcacacgcct | 900 |
| gtaattccag | ctactcagga | ggttgaggca | gcagaatttc | ttgaacctgg | gaggcggagg | 960 |
| ttgcaatgag | ctgagatcgc | gccactgcac | tccagcctag | gtgacagagt | gagactccat | 1020 |
| ctcaaatttg | aaaaaaggag | aaagagatag | agggtagcct | ggaaatcact | agagggtgaa | 1080 |
| cagaggcaaa | tttgcagaac | ctagaaagaa | aaaaacgagt | cagtcacagt | gaactgcaac | 1140 |
| ctaagcaaac | aagcatctta | tgcaactgag | gggaatgaca | tagtaacccc | tgtatccaag | 1200 |
| ggaaggaaac | tgacccttgt | ttagcccat | aatttattca | acccaccag | atgcacacat | 1260 |
| gatcgtggcc | agctcttcta | acattagtat | tttttgccgc | ttcgcagctg | tacctgaaaa | 1320 |
| tccctgatga | atagttgtca | gtctgcagag | cccagggaat | gttagaatgt | aagggtttta | 1380 |
| acacaattta | ttcaaccac | ccagatgcac | acatgatcgt | ggccagctct | tctaacatta | 1440 |
| gtattttttg | ccgcttcgca | gctgtacctg | aaaattccctg | atgaatagtt | gtcagttctgc | 1500 |
| agagcccagg | gaatgttaga | atgtaagggt | tttaacacaa | tttcaaaaaa | aaaaaaaaaa | 1560 |
| tgacttgcaa | actgtatata | aaagcaagca | ctgatgtata | ttcaatttgc | agactacttt | 1620 |
| tccagaaaat | gtcatagtgg | atcttgtcta | gttccaatgt | atctttatgg | tatcaattta | 1680 |
| tctacctagt | gaaattcttt | ccaaatatct | ttttaaat | ttcatataac | tttttttcag | 1740 |
| ggacttttag | tagcagatga | atatcaattt | aaacatttaa | aatatagttg | acccttgaat | 1800 |
| tgcattgggt | cactagtgtg | cagattttct | tccacctctg | ccaccctga | gatagcaaca | 1860 |
| tcaaccctct | cttttctctc | tgctcctcag | cctactgaac | ataaagacaa | ggaggatgaa | 1920 |
| gacccttgtg | atgaccact | tctactcaat | gaaaggtaaa | tctattttct | cttcttatg | 1980 |
| attttctttc | tagctttaag | aatacagtat | ataatactta | tacaaaaata | tgttaattgc | 2040 |
| agagtttgag | accaacctag | aaaacatagc | aagaccctgt | atcctaaaaa | aaaaaaaaaa | 2100 |
| aaaaaaaaaa | aaaaaa | | | | | 2116 |

<210> 42
 <211> 1352
 <212> DNA
 <213> Homo sapiens

| | | | | | | |
|------------|-------------|-------------|-------------|------------|-------------|------|
| <400> 42 | | | | | | |
| ggcagagct | cgtgccgctt | ttttcctgcc | atcggtcaga | aaaaacatgt | cgaagatgga | 60 |
| tggcattaga | ttatgcagga | atttctattg | gaatactggg | ctgctatgtc | tcaggagtat | 120 |
| tttacgcatt | ttattgtaat | aactactggc | gtcagggtgta | cttgatcaca | gtgcttgcta | 180 |
| tgatcctggc | agtgttcttt | gcgcagattc | atcccaatta | cctcacgcag | caatggcaaa | 240 |
| ggctccgctt | tatcatcttt | tgttctgttt | cgggatatgg | agtgattcct | actcttctact | 300 |
| gggtttggct | caatggagga | attggtgctc | ctattgtaca | ggactttgca | ccccgtgtaa | 360 |
| ttgtgatgta | tatgattgct | cttcttgctt | tcctattcta | catttccaaa | gtcccagagc | 420 |
| ggtactttcc | agaatcactt | ccacggtgaa | tcagagaagg | gattgtacca | ctcgtcacgt | 480 |
| gtgttgggaa | agaagaaagg | gtgagaaacc | ctggcctaaa | caatccatcc | cacagatcct | 540 |
| caggcattcc | tttgtgtact | tggtttttca | ccactgagct | ttaaataaga | atggaaatac | 600 |
| aagggaatac | ctgcgtttgt | aacatgagga | tttgggaaca | gatctaggac | atgccactga | 660 |
| attgaagacc | acccatcttc | caggcagggc | cagaattaca | gaaaacaatt | ctggacaact | 720 |
| aaactacctc | ggatcaagcc | accaaataatg | gcatattcctt | gcagtagtga | tgttatattg | 780 |
| gtggcatcag | tcaacagtgt | atgtcatgca | gtacagacat | agcaagcctt | gtcctgacta | 840 |
| tgtttcacat | ttgtgaatta | gaatcaggaa | cgaagattca | gggaatgtct | gtcacatctt | 900 |
| atggcatccc | acctggacag | aatatccgat | ttgaagattg | tgattgactt | ccgtaaaact | 960 |
| gtacaactct | ccattttggca | gctgctacat | aataggtgct | taatgtttgt | ggtgtgaatg | 1020 |
| aaataactga | atttgaatag | aagtttacat | ccaaaagtca | taataagaca | aataatgaaa | 1080 |
| aactccaaag | tcactgatta | taaagaatat | gcaatccatt | tgggatttat | tgcattttaa | 1140 |
| gaaaacagat | taaaacagtg | cttacgtgaa | gtacccaaaac | ctaaaataaa | ccaagcagag | 1200 |
| tagctgactt | gtaagaaaac | tgctctgcct | ggtgaacttc | agcatagaag | agtgggctcc | 1260 |
| accttagatt | ttccaccagc | aagaggacaa | cagtctatca | ctcttaaaaa | ataaacaggg | 1320 |
| taagactgaa | aaaaaaaaaa | aaaaaaaaaa | aa | | | 1352 |

<210> 43
 <211> 1532
 <212> DNA
 <213> Homo sapiens

| | | | | | | |
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| <400> 43 | | | | | | |
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| | | | | | | |
|-------------|-------------|-------------|-------------|-------------|-------------|------|
| cgagaggggac | ccgccccg | ggcctggctg | gctcagggct | acctccttcc | gcctaggacc | 120 |
| cccccttcgg | tgactcccga | ttccctgtcc | taggctgcgg | tgccccggga | ggcgggtcgc | 180 |
| cagagtagca | gacagagctc | tttaatgggt | gtcttctagg | gcgggtgctg | tttgtgcac | 240 |
| atttgggttc | ccacacactt | cctatgaggt | ggcgaaagcc | attatgccta | tgggtgtctgc | 300 |
| tcacacaggg | ggaaactgag | gcccaggcag | gacagcccct | tgccctgggt | gggggctggg | 360 |
| ttgtcccttag | gcctgtgact | tcacctctac | agcaccctcc | tgtggaccct | ctccctgccc | 420 |
| ccgccaggcc | agagtccctgc | agccaggccc | agaccctggc | ctgtccgtcc | ggggatgctg | 480 |
| gacagtactc | ctccctccag | ccctcataag | tcattgtcat | tcggatctgc | atttccccag | 540 |
| ccccctcctc | tctaactggg | gggcactgtg | gcccactgtg | cccccttctc | ttccccattcc | 600 |
| ttccccctac | acccattcca | gacatcccag | agttaacaaa | acccaaaaga | aagagaaaaa | 660 |
| agactcagag | ctgcttggag | gagatgacat | cctcaaagtgt | agcgcctgtg | tttgaggggc | 720 |
| tggtcccagg | cagctttctc | tgtggccttg | ggtgtgcgtt | ttgggtccca | gcgtgatttg | 780 |
| aaagaagatg | gaggttcagc | gaagcagaaa | ggaggtcttg | gaatatgtga | ggcctgttcc | 840 |
| agatggcagg | tgcgactcgg | tgggtggcgt | ggcggcgcca | gctacgcgt | aacagtggga | 900 |
| gattgtgcac | aaggggtggag | aagagggggc | agatggcctg | tcggagccag | agggcatctc | 960 |
| tctgaagcgg | gtcgctgtgg | tgggaagattt | ctttgacatc | atctactcga | tgcatgtgga | 1020 |
| gagctcagcg | gagccaggca | aagcccccaa | gcacgtggg | cagaagaaaa | cctaccgagc | 1080 |
| gatcgacagag | acctatgcct | tcctcccag | agaggccgtg | acccgggtcc | tgatgagctg | 1140 |
| tacggagtgt | cagaagagga | tgacttttaa | ctccaatggc | ctggaacca | aagaaaacga | 1200 |
| gcctccatct | ccactgggtc | ctgggattat | tgattacaac | atgcccctca | cctccacctc | 1260 |
| cctgaagcag | atgaagcttc | gagtgatgaa | ttcccaggag | cagccatcct | cactgtctcc | 1320 |
| ggcacctggc | ttcgtaaaca | ctgttatcac | cgtgctcatc | tgtgcccattg | aagaatgaag | 1380 |
| cacaaaaccg | cacaaacagc | cggaaagcaca | gacccctggg | tttgtttcat | acagaatggc | 1440 |
| actaaatcca | ggtcacctag | aaaaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | 1500 |
| aaaaaaacaa | aaaaaaaaaac | aaaaaaaaaaa | aa | | | 1532 |

<210> 44
 <211> 1300
 <212> DNA
 <213> Homo sapiens

| | | | | | | |
|------------|-------------|------------|------------|-------------|------------|------|
| <400> 44 | | | | | | |
| ggcacgaggg | gaaagcctgg | gcttttgacc | tgtccttgga | ggcgttgccg | cggactttta | 60 |
| tcctctcctt | gggggtccgtg | gcgttctggg | agctgctgac | agcgcctctg | gagcagggtg | 120 |
| cagatgacag | cctttatgag | ttcctggatt | ttgtggatgc | cactgaccga | tacagaagcc | 180 |
| tgtgggtctg | gaggttgctg | ggcatgtcgg | caggcgtggt | tggcatcaca | gccttgggtg | 240 |
| ggcagctgga | ctgcttcctg | atgaccagtg | gcccccgagg | tgtgggtccac | ttctatgggt | 300 |
| actcggtggt | cagcaccctg | gccttactgg | tgagcattgc | ctttcccat | cccatctgtc | 360 |
| agcagtggga | gcccagctac | aaaagggtca | aagcactgtc | cattgtgggg | ggtgaccccc | 420 |
| acctcattct | cctcgcctcc | accactgttt | tggtaggagc | catcgctcag | actgtccaga | 480 |
| actttctgtt | ctggcacatg | aaggaccatg | ggagcggcga | gctgggtcatg | ggtttctcgg | 540 |
| tcgccttcag | cttgctgggg | gaaattctgc | ttcatccgtt | caaagctaca | ttgcttagga | 600 |
| aactgtccag | gacgggcctg | gtggggctgg | ggctgagctg | cctcgctggg | cagctgctgt | 660 |
| actactcttt | cctctggagc | tgggtgtccg | tcctcccat | tcagatcttg | agtgccatta | 720 |
| gcaacagagc | tttgtgtggg | gctgtggggg | cctcagtaga | ggacctggcc | actccccgca | 780 |
| tggagagggc | tctgagtgcc | ttgttccgag | gccactttta | cgggagtggc | tgtagcctgg | 840 |
| gcagctttgt | cgggggcttc | gtggtgatgc | gcttcagcct | ggctgtgctc | taccaggcct | 900 |
| gctgtgtggc | cctgttgctc | tggttggcct | tgctcctgtc | catacagcgg | aggctgcccc | 960 |
| gagagcggaa | aatcaagtac | tcgaagctgc | tgtccatgga | ggtgagtgc | accagtgcct | 1020 |
| ctgagcaggg | gacagaacag | gactggcttg | tgaaggccat | gagggaggaa | cactcagact | 1080 |
| gaaagggctg | agaaatccag | agtgtgctga | tccagcaagg | aacgaatgga | ctgaacaaaa | 1140 |
| ctcagcctgc | tgaggacaga | aacctgccct | ggactgctgg | gagccgggga | agagaggatg | 1200 |
| ggtctgtgct | gaaggcccaa | caggatcatc | tcattgcatg | attttcttta | cttttgaagt | 1260 |
| aaaaggagat | ttaactttta | aaaaaaaaaa | aaaaaaaaaa | | | 1300 |

<210> 45
 <211> 2564
 <212> DNA
 <213> Homo sapiens

| | | | | | | |
|------------|------------|------------|------------|------------|------------|-----|
| <400> 45 | | | | | | |
| ggcacgagga | cgtgctggga | tgtgctggcc | aagccttgct | ggtctgccac | cttgtcctcg | 60 |
| cccctgaagg | gctccagtag | ccagcgaggg | ccagcatggc | ctcccccgcc | ccagcatggc | 120 |
| tggggtctct | gctttcatgg | actgtttgtg | ggtggggtga | ggtgggtcag | ggtcctcctt | 180 |
| gtgctgtgtc | tgcttggggc | tgctcgtggg | caacgtgggt | cactccctct | gtcgtgggtg | 240 |
| agctggcacc | atcaggtgct | gttcaaacc | ctctgagccc | cgagctgctt | gtgatctcat | 300 |

| | | | | | | |
|------------|-------------|------------|-------------|-------------|------------|------|
| ttcaactcca | tgcagccctt | ctagggcagt | tttatttccc | catttttacag | atgggaaaag | 360 |
| agaaactcag | attgcgtaac | atgcccaagg | aagcaccggt | cccagtggtt | tgttttgttt | 420 |
| tgttttgttt | ttgaggtgga | gtctctgtca | cccaggtggg | agtgtctggag | tgagtggttg | 480 |
| caatcttggc | tactgcaag | ctccgcctcc | caggttcatg | ccattttcct | gcctcagcct | 540 |
| cccagtagc | tgggactaca | ggcgcccgcc | accacaccct | gctaattttt | ttgtgttttt | 600 |
| tgtagagacg | gggtttcact | gtgttagcca | ggatgggtctc | aatctcctga | cctcgtgac | 660 |
| cgctgcctc | agcttcccaa | agtcttggga | ttacaggtgt | gagccatggc | gccaggcccg | 720 |
| gtcctagtgt | tgacaggcag | gatcccaccc | caaattggatc | atcatttcgg | tccttcattc | 780 |
| agccacctga | ccctgttttt | ccaggcatca | gggttgccagc | ccacagaggc | actcagacag | 840 |
| ggagggccca | ccagctcctg | ggtgcggggg | gctccagaat | ggagagcgaa | attccctctg | 900 |
| cctgcacaga | gaggctccat | ggaggctttg | atagggctgg | ggtggctgtt | tcatttcagc | 960 |
| tgggtatgc | aatggcagga | agagtctttt | gggagagaga | ggtttaggaa | gcgggcatc | 1020 |
| ctggcctatg | gagggcactc | catgggaggg | gctccatgtg | tccaggggag | cctgagtagg | 1080 |
| cagggagggg | atgagtgaga | ttggcctgga | gataccgggc | ctttagccct | ggagtggagt | 1140 |
| gtttgtcttt | tattctgaga | gcttggggag | gaaggtgctg | gatcaggttt | gagacacatt | 1200 |
| gagctgagag | gagcgtggga | catcagcagg | gacatgccca | ttgggtcttg | agctcaagat | 1260 |
| gggatctggc | ctatgggtggc | cattaggggt | gtcagcagta | caggtctgag | ttggatttgg | 1320 |
| tgcccggtcg | caagttgcat | cgaagctagt | ctcgggtcag | tggctttgca | gggtagggca | 1380 |
| gggacacccg | gggtctcaagc | cgaagaccct | cattgtgcag | atgggcccag | agcaagcaag | 1440 |
| acttccccag | ggcatgccca | gcacaaggcg | gctggagcca | aagccaggca | cccgcgtcct | 1500 |
| gccaggtacg | tcctggacct | gcgtgcctc | atggcatgtc | tggttgtctc | ctgccacctg | 1560 |
| cggaccctgt | gaggcccagc | accagcaagg | gtgaccagc | ccctgctcag | aatggaggag | 1620 |
| agatggagg | ccccagaggt | gcactagac | cccatttcca | agggggccct | ctcagtgagg | 1680 |
| agcagggagc | atttttgtcag | aaagggcagc | ctctggagg | ttgtgggtgac | tgcttgctcc | 1740 |
| tggagttttc | tgtgtcagag | cctctttggg | cagataaate | agttgtgttt | ctgcagcgct | 1800 |
| tgctgcctt | ctccttatga | cttctgtttt | gatgttggga | ggaaagaagt | ctcgtcccc | 1860 |
| ccagatcgag | aggaagtcta | gctgcacctg | actctgggaa | ctccgcctct | gcatctcttc | 1920 |
| tgcttgggtg | gtgtgaaaac | acggccagtg | ggagcggggc | tctggcgta | cagacatcag | 1980 |
| aactgcagac | acctggccca | ggtgtccgtg | ttctgtgtgt | cctgcggcca | ccgaggctgc | 2040 |
| tcacagacat | gagaggccat | tccccacca | gaaccattgg | tgacaaacag | gcagcctcct | 2100 |
| ctaacctccg | caggatgggg | cccggcctgg | cagctgcccc | cagtggccaa | cgtgggcctc | 2160 |
| tgtggacaag | acaggtgcag | ctaaggctgc | aggtgcaaag | caatcccagg | gtgggcgggc | 2220 |
| agggggccac | ctgaacctct | gtacagcaaa | acagtggttt | cctgggatct | ccctcttctc | 2280 |
| gttgttctgt | gaaagcacct | accagccatg | tgaaaagcca | cccggctaac | caccacatg | 2340 |
| caggcgtctg | gcacaggggt | gctcactggc | cgttcagggg | tcggcccttc | ctgatgtttg | 2400 |
| catgtcccc | ttgtgtgaaa | ctcagattta | atttggtgat | tattaaagtg | caggaacctg | 2460 |
| gggctggtag | aggttttttg | tccacagatt | ttgcaaagtg | ccgttaaaaa | aaaaaattca | 2520 |
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<210> 46
 <211> 2594
 <212> DNA
 <213> Homo sapiens

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| ctcttctctc | ctcttgtgtt | ctgagccaag | gtacgcagtt | tctgggtcac | atctccaacc | 120 |
| agtctcctaa | agtgtgttga | ccaaaggtgt | tgctgagttt | gaacacattg | catattttaa | 180 |
| ttgcaatagg | acatgtgggt | gagcaagtta | gttattttgt | ctctatggga | cagctttgcc | 240 |
| attctccttc | ttgtcttccc | agtggggcat | tctgcctttt | gttaagcagt | gttctgggaa | 300 |
| ttatagttct | gaattocact | gacacaatct | cctcttccca | ccctccgctc | tcctcaaact | 360 |
| tgccctcatg | gggtacact | accacaaagg | cacatctctc | cttagggctg | gtgggctttg | 420 |
| ctgggaagaa | gaacatgaaa | gaattgtatg | tagagagttc | cagaagcttc | tagacatttc | 480 |
| ctggtcgtgg | tgggtgtggg | gggttttctt | gaggtcacaa | atatgttcag | atttctcca | 540 |
| tatagctctg | tattttattg | tttctgtatt | cttgtatggg | tgactttgag | tgattcccag | 600 |
| gatatttacc | ctgctattgt | cttaccataa | tcttgatgtg | tctagcctct | tacaaatgag | 660 |
| aaaatcctac | cgaggaatth | cccattttgt | atagtttgtc | ttggggagca | aagaggagga | 720 |
| tagccaatga | tcatgatgat | ctcctctttt | tctacgcaga | gcaggtgttc | atgataaaaa | 780 |
| gcaagtcttt | tgtgtcttca | tgatctgaag | agaggaacaa | acacggatca | agatgatcct | 840 |
| agacctccta | atcatgggga | tgattacaag | gagttgcaga | ccctactctc | tattttgcag | 900 |
| tgggtggagt | tgtggatagg | ggtgacccat | cagtcattga | gaaatgaatc | tcctgggtgc | 960 |
| tacttgtgaa | agtgaggatc | ctctctccct | ttctgttgga | tcagctgag | attctggaca | 1020 |
| gcctagactt | cttctcaggt | gtcagagtaa | gattgcctca | atggggcggg | gcaggacaca | 1080 |
| ctgctgacct | caccactggg | cgccctgggc | agccactgcg | aggcctcgtc | attttcgagt | 1140 |
| tgggtgagaca | ccgcggcaggt | cgacttgaa | gatgctctgg | tggtagaggt | tagattattt | 1200 |
| gtagttttgg | gggccttttc | ttcaaataac | tgggaatttc | attgaaaata | tgtagttcag | 1260 |

| | | | | | | |
|-------------|-------------|-------------|-------------|-------------|-------------|------|
| gagtgaaggg | gtctatatctc | tactttataa | ttatcattat | cattttggta | tcttttggga | 1320 |
| gaatggccta | aaattgggac | caagatggaa | aagaagggaa | aggaatgggt | caatattaga | 1380 |
| atgcccttcg | ttatcctttc | aacttggtaa | accagagatt | aataccatag | caccactgtg | 1440 |
| gtgaaagacg | gggtgggcat | tccccaagg | catgaccagc | agacttctct | cagattcttg | 1500 |
| agtgggtcaa | gcagaccatt | ctgggtctggc | ttctcctctc | agattttatt | gagtaatccc | 1560 |
| ctcccttggg | gataagattg | tgtttcagca | agagtggtag | tggtaccatt | tcggaaggag | 1620 |
| taatttttgc | aggggaagtg | gtgggagggg | ggcatagtta | gaacataagg | aggaaacttc | 1680 |
| taaaggcttg | ttagttttatt | ttcagagatt | tcagtacaat | cttgggtaat | ttatggctgg | 1740 |
| cccatctgat | gctctgggtt | atgtttgtaa | acactgggtg | ctaccctccc | tgtccaagat | 1800 |
| ccttgtcccc | ctgtctccat | gccatactct | ccatttttgg | tgctgtctgt | caagtagagc | 1860 |
| ggctgctaac | ttggcaattt | agtaatgctg | tgtaggttg | ggaagaaacc | gatcagaggc | 1920 |
| atggcagccc | ctgggattaa | gttactgttc | taattttacag | tgccctccct | gttgtgacct | 1980 |
| atgctagaat | ctatgtttta | gtctcatctt | ctaaagaata | aatggcatca | gacctgtgct | 2040 |
| tctcttcaac | ctgggtgaaa | tgatccaaat | gaataaatat | ttagggattt | gtgaggtctt | 2100 |
| tgaaagaatt | atattgtttt | actcaaagct | gattttttaat | caactaaaac | ttgctttcta | 2160 |
| gtcaaaactga | gtaagaaagc | tgaacaattc | tagaccatcc | ataacgagag | ctaccgtttt | 2220 |
| tgctataaag | tttttcaggc | tccctttctt | ttcagtaaag | ctgggtccag | ggaaataaatt | 2280 |
| tgctatttac | ttaggtagga | agaaatagtc | tactgcccc | ttttcttaaa | gacagtatat | 2340 |
| gccttcaaaa | atgtttattat | aagcattttc | aagcatatag | aaaagcagaa | aagtgtgtaa | 2400 |
| tgagcatcca | tacacctatc | aaccagatta | aacaattata | tttttccctat | ttgctttctc | 2460 |
| ttttctgttg | aaatatattaa | aaatatagat | aatgttttaa | tgtattttaag | tatgtttaat | 2520 |
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| aaaaaaaaagc | tcga | | | | | 2594 |

<210> 47
 <211> 2030
 <212> DNA
 <213> Homo sapiens

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| ctgggctccg | cgatcctctc | ccccaccctc | gggcaactgt | ccgcctccct | ccggcggggc | 120 |
| tgtccccgca | gtgctccccg | acccggcgag | ccttcggggc | gcgcgtcgct | ggtgggtggtt | 180 |
| gaggctctag | cgataataaa | tgatagagga | tacaatgact | ttgctgtctc | tgctgggtcg | 240 |
| catcatcgcg | tacttcttgc | tgagaccgca | gacgcttttc | ctgctgtgca | tcagcttggc | 300 |
| tctatggag | tacttcttcc | acaccgacga | ggtagaagacc | atcgtgaagt | ccagccggga | 360 |
| cgccgtgaag | atgggtgaagg | gcaaggtagc | cgagatcatg | cagaacgatc | gactcggggg | 420 |
| gcttgatgtg | ctcagaggccg | agttttccaa | gacctgggag | ttcaagaacc | acaacgtggg | 480 |
| cgggtgtactc | catccagggc | cggagagacc | acatggagga | ccgcttcgaa | gttctcacgg | 540 |
| atctggccaa | caagacgcac | ccgtccatct | tcgggatctt | cgacgggcac | gggggagaga | 600 |
| ctgcagctga | atatgtaaaa | tctcgactcc | cagaggccct | taaacagcat | cttcaggact | 660 |
| acgagaaaaga | caaagaaaat | agtgtattat | cttaccagac | catccttgaa | cagcagattt | 720 |
| tgtcaattga | ccgagaaaatg | ctagaaaaat | tgactgtatc | ctatgatgaa | gcaggcacaa | 780 |
| cgtgtttgat | tgctctgcta | tcagataaag | acctcactgt | ggccaacgtg | ggtgactcgc | 840 |
| gcgggggtcct | gtgtgacaaa | gatgggaacg | ctattccttt | gtctcatgat | cacaagcctt | 900 |
| accagttgaa | ggaaagaaaag | aggataaaga | gagcaggtgg | tttcatcagt | ttcaatggct | 960 |
| cctggagggg | ccaggggaatc | ctggccatgt | ctcggctccct | gggggattat | ccgctgaaaa | 1020 |
| atctcaacgt | ggtcacccca | gacccagaca | tctcgacctt | tgacctggac | aagcttcagc | 1080 |
| ctgagttcat | gatcttggca | tcagatggtc | tctgggatgc | tttcagcaat | gaagaagcag | 1140 |
| ttcgattcat | caaggagcgc | ttggatgaac | ctcacttttg | ggccaagagc | atagttttac | 1200 |
| agtcatttta | cagaggctgc | cctgacaata | taacagtcac | ggtgggtgaag | ttcagaaata | 1260 |
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| ccaccccaga | catggaaatcc | ccctccctgt | gtgggtcttag | gtctataatc | agtgacgaac | 1440 |
| agaggggtgcc | cttgggccat | gtagttaaga | aactggaaaa | tggtttcttc | atgttttccc | 1500 |
| aactctttca | tccagtgtcc | aaaatatata | agtaaatagc | tgtagagtca | catatatgaa | 1560 |
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| tcctccaggc | atcagctgtt | gtgtcctctc | tttgtaacag | tggacaggac | agaccaccca | 1680 |
| gtgctgcagg | agacaggcca | ctgcgtcacc | tgtgagtggg | caggggctga | tgtggcaaca | 1740 |
| ccctctgcca | agagacagag | ctgtcctgag | aatgctttgt | ccttctgagc | ccatgttttc | 1800 |
| tgctcagtag | cagcttggaa | gcagatttgg | aatggtttat | tattttggct | gctcttgggg | 1860 |
| actgcgagaa | gcagagagaa | tgagagacca | gtggcaactg | cctgcacagc | agagataacc | 1920 |
| ctctccctt | gcttccttta | atagttaaat | agactttgta | tacaaaaaaa | aaaaaaaaat | 1980 |
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<211> 1602
 <212> DNA
 <213> Homo sapiens

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<210> 49
 <211> 508
 <212> DNA
 <213> Homo sapiens

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<210> 50
 <211> 612
 <212> DNA
 <213> Homo sapiens

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 gtcagtctctg ktgaaagccc cttccattct gaagtgtac gagccccgga ctttgctctg 540
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<210> 51
 <211> 2291
 <212> DNA
 <213> Homo sapiens

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<210> 52
 <211> 2842
 <212> DNA
 <213> Homo sapiens

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| gtcaacctgc | aggaacggaa | gcaggaggtg | gtcgcagcag | tttttggaag | aagcgtagc | 840 |
| aataagtata | cttagaacag | cttgctgtgc | acttaattgt | aacatacccc | atgccaagca | 900 |
| ccttgacaga | agtgtttctc | attcagtcctc | cttaggagcc | cagggaggca | ggaagctttt | 960 |
| gtgggtcccg | ttttataagg | gaggaagctg | aggctcaggt | tgtctagctc | aagggcccg | 1020 |
| aggtctaggt | ggaccctgc | acatccctga | gtattgcgc | ctgggtggag | ctggctccgc | 1080 |
| agactgcga | ggcccacgc | tgtgtagctg | tcacctggac | ccggaggctg | acagctgccc | 1140 |
| tgcctccctg | agctcaggcc | tggcgtgtac | tcaggaaaca | actgtcgcca | ggactgttca | 1200 |
| gggagtgtt | gaggaggatg | aagatggggt | ttgaggccca | gacactctgg | gggtggctgt | 1260 |
| tgtaggtcta | gggcacccca | ctgtggaacc | cagcctgccc | ctgccctcaa | ctgtccccc | 1320 |
| tccctccctg | agcccagaac | tggagaagat | tcgggaactc | agagtttgac | ccccccggac | 1380 |
| ccaatgtggc | caccaccact | gtcagtgcag | atgtctctat | gacgttcac | accagcaaag | 1440 |
| aggacctgaa | ctgccaggag | gaggaggacc | ctatgaacaa | actcaagggc | cagaagatcg | 1500 |
| tgtcctgccc | catctgcaag | ggcgaccact | ggaccacccg | ctgcccttac | aaggatacgc | 1560 |
| tggggcccat | gcagaaggag | ctggccgagc | agctgggcct | gtctactggc | gagaaggaga | 1620 |
| agctgcccgg | aggtgtgggg | gtgggagggg | cctgctgtca | gtgcacgggt | tctgtcccca | 1680 |
| ctgctgcctt | cgtgctgtca | tctcccgcac | gacagtgcag | cgggtttgat | ggtgccagac | 1740 |
| tctcctcggg | gcgtctgtgc | cttectaatt | ggctgtacct | cctatggttg | ggagacgggc | 1800 |
| gctcccata | tatgtgcgac | ttggcagctg | tgactttgct | ggtggccctg | tgactgtcct | 1860 |
| gatgagctgc | tgtctgtcgg | ccccagggtg | ctgaccaccc | cacatcgtgt | gtgcgcactg | 1920 |
| tgtgtatagt | gtctccgttg | catgcctgtg | gctgtaccgt | ccgaattctt | tggtgggatt | 1980 |
| tgctgggtgg | gagtgtgaga | gtgcagacgt | gcacttgtcg | cctgccacgc | gagggggacc | 2040 |
| tgggcgctgt | tcctgtttgt | tgtcccattg | ctgccgttgc | tgtgcatgtg | aggctgccgc | 2100 |
| ccctgtttgt | ctcccgcctt | ctctgggggtg | gggtcggggc | tcctcctcct | cctcctccac | 2160 |
| cagtgtcgtc | ggctgggagc | tcaaattggtg | tcagcttctc | aggtgtcacc | ttggtgtcct | 2220 |
| cgtggccaac | tggctgctgt | tggtttggca | cacagtgcct | gcgctggctc | aacactgaag | 2280 |
| cccagacttc | ctggggcggc | tctgtcccca | cgcttgcgc | acagtgggt | tgaacttgac | 2340 |
| tgtcttttgg | tccccagagc | tagagccggt | gcaggccacg | cagaacaaga | cagggaagta | 2400 |
| tgtgccgcgc | agcctgcgcg | acggggccag | ccgccgcggg | gagtccatgc | agcccaaccg | 2460 |
| cagagccgac | gacaacgcc | ccatccgtgt | caccaacttg | tcagaggaca | cgctgagac | 2520 |
| cgacctgcag | gagctcttcc | ggcctttcgg | ctccatctcc | cgcactacc | tggctaagg | 2580 |
| caagaccact | ggccaatcca | agggcttcgc | cttcatcagc | ttccaccgcc | gcgaggatgc | 2640 |
| tgcgcgtgcc | attgccgggg | tgtccggtt | tggctacgac | cacctcatcc | tcaacgtcga | 2700 |
| gtggggccaag | ccgtccacca | actaagccag | ctgccaccgt | gtactcggtc | cgggaccctt | 2760 |
| ggcgacagaa | gacagcctcc | gagagcgcg | gctccaagg | caataaagca | gctccactct | 2820 |
| caaaaaaaaa | aaaaaaaaa | aa | | | | 2842 |

<210> 53
 <211> 765
 <212> DNA
 <213> Homo sapiens

| | | | | | | |
|------------|-------------|------------|------------|------------|------------|-----|
| <400> 53 | | | | | | |
| ccacgcgtcc | ggtgataaaa | gtccttccag | tcccatctgt | gtggctgtca | cttcttcttc | 60 |
| ccctgtcctg | ctactccaag | cacagtcatt | cctccaaagt | gctgggttcc | tcctggccca | 120 |
| gccggggcca | ttccttagtg | ggcattatcc | ttgcaagtgt | gagagccaga | gaggggcatg | 180 |
| tgtagtatcc | atgtccacaa | acagggtccc | atcctccttt | gtgtggtttc | tgtgtctagc | 240 |
| atgtcatctt | ccttccctgcc | cctctgcaac | tcagggaatt | gctgtcttta | taccaagta | 300 |
| tcacagcagc | agaattgggg | ctgccccatg | ctccatctcc | ggtcatggtg | gtatcaaagg | 360 |
| caacacctgc | caggacaatg | ctggttatga | tttctgcgt | cccctgggac | tggcctcatt | 420 |
| ccttaagagg | caagattaaa | aaaaaataaa | aagccaggca | cgagggtcca | tgcctataat | 480 |
| cccagcactc | cagcactttg | ggaggccaaa | gcggaggatt | gcttgaactc | aggagttcga | 540 |
| gaccagcctg | ggcaacatag | cgagacccca | tctctacaaa | aaatttaaaa | atgaggcagg | 600 |
| tatggaggta | tgcgcctgtg | gttccagcta | ctcaggaggc | tgagggtggg | ggattgctag | 660 |
| agcccaggaa | gttgaggctg | cagggagccg | tgattgcacc | actgcactcc | agcatgggca | 720 |
| gcagagtaag | aacctgtctc | aaaaaaaaa | aaaaaaaaa | aaaaa | | 765 |

<210> 54
 <211> 1896
 <212> DNA
 <213> Homo sapiens

| | | | | | | |
|------------|------------|------------|------------|-------------|-------------|-----|
| <400> 54 | | | | | | |
| tcgaccacag | cgtccgggga | ctccctggga | gatgaggccg | cgagggtctcc | cgccgctcct | 60 |
| ggtggtgtct | ctgggtgtgt | gggcctccgt | gagcgccag | accgatgcca | ccccggcggt | 120 |
| gacgacagag | ggcctcaact | ccaccgaggc | agccctggcc | accttcggaa | ctttcccgctc | 180 |
| gaccaggccc | cccgggactc | ccagggtccc | agggccctcc | tccggcccca | ggcctacccc | 240 |

| | | | | | | |
|-------------|-------------|------------|-------------|-------------|------------|------|
| agtcacggac | ggtgctgttc | tctgtgtctg | tgacttatcc | ccagcacagt | gtgacatcaa | 300 |
| ctgctgctgt | gatcccgact | gcagctccgt | ggatttcagt | gtcttttctg | cctgctcagt | 360 |
| tccagttgtc | acgggcgaca | gccagttttg | tagtcaaaaa | gcagtcacat | atcatttgaa | 420 |
| ttttacagca | aaccacacct | aaagagtatt | tgaacttggt | gaccagatta | atccatctat | 480 |
| tttctgcatt | catattacaa | actataaacc | tgcattatcc | tttattaatc | cagaagtacc | 540 |
| tgatgaaaac | aattttgata | cattgatgaa | aacatctgat | ggttttacat | tgaatgctga | 600 |
| atatatgttt | ccttcacaac | caaactggat | attcctactg | ctgctaaata | tgagtatggg | 660 |
| gttctctctg | agacttcaga | ttcgtttctg | agattttcctt | cgtccctgac | atcatctctg | 720 |
| tgcactgata | ataaccctgc | agcgtttctg | gtgaaccagg | ctgttaagtg | caccagaaaa | 780 |
| ataaatttag | aacagtgtga | agaaattgaa | gccctcagca | tggcttttta | cagcagcccc | 840 |
| gaaattctga | gggtacctga | ttcaagaaaa | aaggctcccta | tcactgttca | gtccatcgct | 900 |
| attcagcttc | taataaaaac | gctcaccgga | cgaggaggaca | ctgatgtgct | gcagccgact | 960 |
| ctcgtcaacg | ctggacactt | tagcctttgc | gtgaatgttg | ttcttgaggt | aaagtacagc | 1020 |
| ctcacatata | cagatgcagg | tgaagtcacc | aaagctgac | tctcattcgt | tctggggaca | 1080 |
| gttagcagcg | tagtgggtccc | actgcagcaa | aagtttgaaa | ttcattttct | tcaggaaaat | 1140 |
| accagccag | tccctctcag | tggaaaccct | ggttatgtcg | tggggctccc | attagctgct | 1200 |
| ggattccagc | ctcataaggg | gtctgggatt | attcagacca | caaatagata | tggacagctt | 1260 |
| actattcttc | atagcacaac | tgagcaagac | tgcttagcac | tggagggggg | ccggaccoca | 1320 |
| gtattatatt | gttacactat | gcaatctggc | tgtaaactaa | gactgactgg | agctctcccc | 1380 |
| tgtcagctcg | tagcacagaa | ggtgaagagc | ctgctgtggg | gccagggctt | cccagattac | 1440 |
| gtggccctt | ttggaaattc | ccaggcccag | gacatgctgg | actgggtgcc | catccacttc | 1500 |
| atcacccagt | cattcaacag | gaaggattcc | tgccagctcc | caggggcttt | ggttatagaa | 1560 |
| gtgaagtgga | ctaaatacgg | atccctgtcg | aatccacagg | ccaaaatagt | caatgtaact | 1620 |
| gcaaattctaa | tttcatactc | ctttcctgag | gccaaactcag | gaaatgaaag | gacgattctt | 1680 |
| atttccactg | cggttacttt | tgtggatgtg | tctgcacctg | cagagggcagg | cttcagagct | 1740 |
| ccaccagcca | tcaatgccag | gctgcccttt | aacttcttct | tcccgtttgt | ttgacaatgc | 1800 |
| tcagatgcat | cagttcctta | atatacacgt | gaaatttgaa | aactgtacat | tcggtgagat | 1860 |
| taaattttat | atacaactag | caaaaaaaaa | aaaaaa | | | 1896 |

<210> 55
 <211> 1876
 <212> DNA
 <213> Homo sapiens

| | | | | | | |
|------------|------------|------------|-------------|-------------|------------|------|
| <400> 55 | | | | | | |
| tcgaccacg | cgtccggtgg | atgaatgggt | ttgatagttg | tgcttctatt | tcccaacctc | 60 |
| tgtatgtgta | cctttcatgc | aggtggattt | cagtgtgttc | tttggatggc | aggccttaag | 120 |
| agaagagtcc | cactgcacag | cctcagatac | ttcatctcca | tgggtgggtct | cttctccaaa | 180 |
| ccaggactgc | ttccctggta | tgccagaaat | ccaccaggat | ggtcacagct | ctttctgggc | 240 |
| acagtatgta | agggagattt | cacccgtgtg | atagccacga | aatgtcagaa | aggacaaaaa | 300 |
| agtcagaaga | aaccaagcca | tcttggacca | ctagatgggt | cctggcagga | aaggctggct | 360 |
| gatgttgtga | caccactctg | gaggttgagc | tatgaagaac | agctcaagg | gaaatttgca | 420 |
| gctcagaaga | aaattttaca | aagactagag | tcttacatcc | aaatgctcaa | tggagttagt | 480 |
| gtgacaacgg | ctgtacccaa | atctgagagg | ctctcttgct | ttctccatcc | tattataccc | 540 |
| ctctcctgtc | atcaatgggt | accgaaataa | gtccaccttc | tctgtgaacc | gaggtccaga | 600 |
| tggcaatcca | aagactgtgg | ggttctaccc | gggaacttgg | agagatggga | acgttgtctg | 660 |
| tgtgcagtct | aatcatctga | aaaacatccc | tgagaacac | agtcaagtgg | cgcagtacta | 720 |
| tgaagtattc | cttcgacagt | ctccattgga | gccctggcct | gtatttcatg | aaggtggata | 780 |
| ctggcgtgag | ctcacagtc | gcaccaatag | ccaagggcac | acaatggcta | tcatcacttt | 840 |
| ccatccccag | aaattaagtc | aggaggagct | ccatgttcag | aaggagattg | taaaggaatt | 900 |
| tttcatcaga | ggctctggag | cagcctgtgg | cttgacctca | ctttacttcc | aggaaagtac | 960 |
| catgacccgt | tgcagccatc | agcagtctcc | ctatcagctt | ctgtttgggg | aaccctacat | 1020 |
| ctttgaagaa | cttctgagct | tgaagatccg | catctctcca | gatgcctttt | tccagattaa | 1080 |
| cacagctggt | gcagagatgc | tgtatcggac | tgtgggggag | ctgactggag | tgaactctga | 1140 |
| caccatcctt | cttgacatct | gctgtggaac | tgggtgtgatt | ggcctctctc | tggctcagca | 1200 |
| tacatctcgg | gtccttggga | ttgaattggt | ggagcaggca | gtggaggatg | caagatggac | 1260 |
| tgcagccttc | aatggcatca | ccaactctga | atttcatact | gggtcaagcag | agaagatttt | 1320 |
| gccagggtcg | ctaaagtcaa | aggaagatgg | acagtcaatt | gttgctgtgg | tgaacccagc | 1380 |
| ccgtgccgga | ctgcattaca | aggtgattca | agccattcga | aacttcaggg | ccatccacac | 1440 |
| gctagttttt | gtttcctgca | agctccatgg | tgaatccact | aggaatgtca | ttgagctgtg | 1500 |
| ctgtcctcca | gaccttgcta | agaagctctt | aggcgagccc | tttgtcctgc | agcaagctgt | 1560 |
| acctgtggat | ttgttccctc | acacccca | ttgtgagctg | gtgctcctct | ttactcgata | 1620 |
| agcagcctgg | gtgacagagt | gggacaccat | ctcaaaaaaa | aaaaaaaaaa | gaaaatgtag | 1680 |
| ttatccctag | gagcaatagc | accaattaac | tctcacccgt | ggaggaagaa | ttggttattg | 1740 |
| gagagaccct | aagggaaagg | agattttcag | agagactgaa | tacctataat | tgtgctgtgt | 1800 |
| agtgtggagg | caaaaagctc | caaaatctag | tataacataa | taaactggat | attgaaaact | 1860 |

gaaaaaaaaa aaaaaa

1876

<210> 56
 <211> 1072
 <212> DNA
 <213> Homo sapiens

<400> 56
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 cttgaagagc aaactgtcag gaaatgtcca acacaaatgg cagtgcatac acagaattca 120
 ttttactttg gctcacagat tgcccgggaa tccagtcctc gctttttgtg ctgtttcttg 180
 ttgtttacct cgtcacacct ctaggcaacc tgggcatgat aatgttaatg agactggact 240
 ctgcgcttca cagccccatg tacttcttcc tctaactt agcctttgtg gatttgtgct 300
 atacatcaaa tgcaaccccg cagatgtcga ctaatatcgt atctgagaag accatttcct 360
 ttgctgggtg ctttacacag tgctacattt tcatgtccct tctactcact gagttttaca 420
 tgctggcagc aatggcctat gaccgctatg tggccatata agaccctctg cgctacagtg 480
 tgaaaacgtc caggagagtt tgcactctgt tggccaccat ttccctatgt ctatggcttc 540
 tcagatggac tcttccaggc catcctgacc ttccgctga ccttctgtag atccaatgtc 600
 atcaaccact tctactgtgc tgaccgcgcg ctcatlaagc tttcttggtc tgatacttat 660
 gtcaaagagc atgccatgtt catatctgct ggcttcaacc tctccagctc cctcaccatc 720
 gtcttgggtg cctatgcctt cattcttgct gccatcctcc ggatcaaata agcagaggga 780
 aggcacaagg cattctccac ctgtgggtcc catatgatgg ctgtcaccct gttttatggg 840
 actctctttt gcatgtatat aagaccacca acagataaga ctgttgagga atctaaaata 900
 atagtgtct tttacacctt tctgagtcgg gtacttaatc cattgatcta cagtctgagg 960
 aataaagatg tgaagcaggc cttgaagaat gtcttgagat gaaatattgt catgaccatg 1020
 gtgatgcctt tgtttcctaa taaacattaa atcgaaaaaa aaaaaaaaaa aa 1072

<210> 57
 <211> 652
 <212> DNA
 <213> Homo sapiens

<400> 57
 ggcacgaggg acgtgaaaaat ctgccttctc accatgagggc ttctagtcct ttccagcctg 60
 ctctgtatcc tgcttctctg cttctccatc ttctccacag aagggaagag gcgtcctgcc 120
 aaggcctggg caggcaggag aaccaggctc tgctgccacc gagtccttag ccccaactca 180
 acaaacctga aagccttcac agcagtgagc tgcaatgttg gagggcttca tctcgggctg 240
 caaggaccct gggaaagtcc cagaactcca cgtccttgct tcaattgtgc catcaacttt 300
 cagagctatc atgagccaac ctacccccac agggcctcag tcgccaccat gtgggcctct 360
 ccagtgcata ccaccgagca ttccaccatg accggtcaca gctacaaatc cagagaccat 420
 caatctctgt agagtgcagg gtggcaagca cccaagggg gctgaccaag actgcagagt 480
 ctctctccat ttaccgtcca ttcagcctcc tggcatltaa ctaccagcat ccagtgggtc 540
 ccaaggaatc ccttcttagc ctctgacat gagtctgctg gaaagagcat ccaacaaac 600
 aagtaataaa taaataaata aactcaaaaa aaaaaaaaaa aaaaaaaaaa aa 652

<210> 58
 <211> 1352
 <212> DNA
 <213> Homo sapiens

<400> 58
 ccacgcgtcc ggaacgcagc aggttgtccc agctttcgtc ctacgcgccag cgcggaggag 60
 gcgatgtctg ggctgtctcg cccgctgctt ttggccgtcg gctgcctggc cgcgctctgc 120
 gtaatcacag cgggtgggaa caccacctg gccccgaacg tgactacagc ctgctctcca 180
 ccgcccacca ccacgacagt cccggtgtca ccgacgactc tctcgcgctg gccggtcacc 240
 actccagcac cagatatctg tgggaagccg aacagttgtg tttcctgtgt tgatggtaat 300
 gctacctgct tttggataga atgtaaaggt aaaagctact gttcagataa ttcaacagct 360
 ggtgattgca aggtggtgaa caccacagga ttctgttctg ctaaaaccac aactctgcct 420
 tccactacta caacttccac cacagctact acatcaggta caactaatac cactctatct 480
 ccaactatac aacctacgag gaagtctacc tttgatgcag ccagtttcat tggagggaatt 540
 gtccttgtct tgggtgtgca ggctgttaatt ttctttctct ataaattctg caaatctaaa 600
 gaacgaaact accacactct gtaaagagac ccactaaatt aacaaggact ggcgtgtaac 660
 tcaactgaaac caaaatatta tctttcaaga tgtcccatat ggaagacgct attctaggat 720
 ctttaatttt tcaaaggatg catataggag catcaccctt gaagaagaat cagttcagtc 780
 actttgctca acgggcctat ttaaagtacg ctgcatgagt ccttgtggct gtctttcatt 840

| | | | | | | |
|------------|------------|------------|------------|------------|------------|------|
| ttacatggct | gctgctgtgg | gattgtgttc | tctctgcttg | acatgccaaa | tgtaacttta | 900 |
| agtgatggaa | aacattgtcc | tgcgcagaca | accteatgac | tcttttggca | atttaaagt | 960 |
| aatcatttta | agcctgaaag | ctgcattatt | ttcatcctaa | ctcaggatgt | agtttagtga | 1020 |
| ccagaattga | gaagaatgtg | ccaaagagc | atcagtcagg | tggatttttg | gctatcgttt | 1080 |
| caaaagtggg | ataaatttat | aaatttagta | ccttagagt | aaaattttgt | gcttgataac | 1140 |
| agttattttt | tttctacatt | agaaaaaaag | atgccacaca | gggaattaca | ttccagattt | 1200 |
| aaagaaatga | gaggatacac | aacatgaaaa | gtatagcagg | ttattgttca | tacttgtaaa | 1260 |
| gcaccttata | tcattgagaa | ataaagaaca | gtgccttaaa | aaaaaaaaaa | aaaaaaaaaa | 1320 |
| aaaaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | aa | | | 1352 |

<210> 59
 <211> 1335
 <212> DNA
 <213> Homo sapiens

| | | | | | | |
|------------|------------|------------|------------|------------|------------|------|
| <400> 59 | | | | | | |
| ctggcaggct | gggggctctg | ccaggacagg | gaggggcctg | ggcctggcca | gaccagaggg | 60 |
| caggttgaga | cctggaggca | gggtccactg | tggtcacacg | gggccaccct | gctctggctc | 120 |
| ttgagtctca | gaatccgaat | cgtgaacttc | gttgtcatga | acaacaagac | ctcggctggg | 180 |
| ggtaagggca | gggggtgggg | actgacaggg | gcgctgcggg | cagggttctc | ccagcacctc | 240 |
| actccccctg | actcgtgaac | ccctgtgacc | cagagacctt | cgaggatctg | atgaaggacg | 300 |
| gggtctttga | ggccagggtt | cccctgcaca | aggtgarggg | tkggcyggcc | tggagarggc | 360 |
| cctgggggtg | gacctggga | tkggggtct | cactctctgt | caccgagcc | agggggagg | 420 |
| acgcctggg | aagacgtggg | cgcggtggag | acacatgttc | cgggagcagc | cagttgatga | 480 |
| aatcaggaac | tactttgggg | aaaaggtggc | cctgtacttc | gtctggctgg | gctggtacac | 540 |
| ctacatgctg | gtgccggccg | ccctgacggg | cctcttagtc | tttctgagcg | gattctcgct | 600 |
| gtttgaggcc | agccagatca | gcaaggagat | ctgtgaggcc | cacgacatcc | tcattgtgtc | 660 |
| cctcggcgac | cacagccgca | ggtaccagcg | gctctcggaa | acctgcactt | ttgccaagct | 720 |
| caccaccttc | tttgacaatg | atggcacggt | ggtgttcgcc | atcttcattg | ctctctgggc | 780 |
| cacggtgttc | ctggagatct | ggaagcggca | gcgcgccgcg | gtggtcctgc | actgggacct | 840 |
| gtacgtgtgg | gacgaggaac | aggtgaggtg | gagctggcag | cgcagctgag | gccgaccgca | 900 |
| gcaggggctg | ttggcgcccc | atgccctgca | cggcccatat | atgcctgcg | tgtctgagga | 960 |
| ggaaatggca | cttcagctca | ttaactgccc | cgactacaag | ctccggccat | accagcactc | 1020 |
| ctacctacgc | agcacctgca | tcctcgtcct | gacctgtctc | atgatctgcc | tcattgatcg | 1080 |
| catggcccc | gtcctggwgg | tctaccgcgt | cctggctccg | cgctcttcag | cagctcggcg | 1140 |
| tgcctttctg | gaggagcagg | tgaccacggg | cgtgtggwgg | accggggctc | tgggtgacta | 1200 |
| tgtgaccatc | atcatcatga | ccaaagtggg | gccgggagca | rggcargccc | garctggggg | 1260 |
| gtccaccgga | gccccaaagt | agccmattyg | ggkgcccttc | ttcggaagat | caacaggaga | 1320 |
| tgcccaagaa | acctt | | | | | 1335 |

<210> 60
 <211> 2140
 <212> DNA
 <213> Homo sapiens

| | | | | | | |
|------------|-------------|------------|-------------|-------------|-------------|------|
| <400> 60 | | | | | | |
| ggcacgagcc | caggctcaag | caatccttct | gccttgacct | cccaagggtgc | tgggattaca | 60 |
| ggcatgagcc | gctgcacctg | gccttcattt | agtttctttc | tttcttcctt | tctttctttt | 120 |
| tttagatgga | gtctcgctct | gtcagccagg | ctggagggca | gtggcgatgat | cttggctcac | 180 |
| tgcaacctcc | gcctcccagg | ttcaagcgat | tctcctgcct | cggcctccca | aagtgtctgg | 240 |
| attacaggca | tgagccgctg | tgtgtgacgt | catttgggtt | ctataatcac | caaagcccat | 300 |
| ctggtctcat | ggcctttgca | gatgaatata | ctcccttaga | acacatcttc | cccaagagtt | 360 |
| caccttactg | gcaacttctc | atccattagg | cctcagcttt | aatgtatcat | cttcagggat | 420 |
| gcttttactg | tccctccctt | ccagtgtaat | ctagatccct | gtctctatta | cccagcactg | 480 |
| tcaacagata | gaaatgttcc | ctatctgtcc | tgtccaatat | tacagccacc | actgtatgtg | 540 |
| gtcagtgagc | acttgaaatg | tgaactgaat | tttaagattc | gatttaatat | taattttatt | 600 |
| aaatgtaaac | aaccacatgt | ggccagtggt | taccagattg | ggtagtgtag | ctctaaattg | 660 |
| taaattcttg | ctgggcacag | tggctcacac | ctgtaatccc | agcacttttg | gaggcggagg | 720 |
| cgagagggtc | gccttgaggc | aggagttaga | gacaagccta | ggcaacatag | caagactccg | 780 |
| tctcaaaaaa | aatttttttag | taataataat | agtaataact | tgttaagtct | ggccaggtag | 840 |
| agtggctcac | gcctgtactc | cgagaacatt | gggaggctga | ggcaggcaga | ttgcttgatc | 900 |
| ccaggagttt | gagaccagcc | tgggtaatgt | gtcaagaccc | catctctaca | gaaaacagaa | 960 |
| agattggctg | ggcatggttg | tgcacgcctg | tagtcccagc | tactcaggag | gctgatgtgg | 1020 |
| aagaatctct | tgagccgggg | tggctcaggc | tgcagtgagc | tacaatttgc | ccactgcact | 1080 |
| ccagcctggg | caacaaactg | agaccctgta | tcaaaaataa | ataaataagt | tgttaacttt | 1140 |
| gtgagagcaa | ggacagtttc | atcttacata | gtttttaccca | gcaccagca | cgggtgcctgg | 1200 |

| | | | | | | |
|-------------|-------------|-------------|-------------|------------|------------|------|
| ccagaaatgg | gactcatggg | gagttgaaag | ttgggggttc | tctcaagccc | tcgaaaacca | 1260 |
| tccccctcca | aatgccattc | agacgcctga | ccacaagggtg | gctccatgac | atctctggct | 1320 |
| cggagtgga | gtcctgggga | ggtcattcaa | ggaagtggag | atccaagcac | taattttctt | 1380 |
| gggtctctgtg | tctctgggtct | tctcctaagt | cctggagctt | gaaaatctgc | cgcagaatgg | 1440 |
| ccgccagtgt | tacagctgca | aggggaacag | cacccatgga | tgctcctctg | aagagacttt | 1500 |
| cctcattgac | tgccgaggcc | ccatgaatca | atgtctggta | gccaccggca | ctcacgaacc | 1560 |
| gaaaaaccaa | agctatatgg | taagaggctg | tgcaaccgcc | tcaatgtgcc | aacatgcccc | 1620 |
| cctgggtgac | gccttcagca | tgaaccacat | tgatgtctcc | tgctgtacta | aaagtggctg | 1680 |
| taaccaccca | gacctggatg | tccagtaccg | cagtggggct | gctcctcagc | ctggccctgc | 1740 |
| ccatctcagc | ctcaccatca | ccctgcta | gactgccaga | ctgtggggag | gcactctcct | 1800 |
| ctggaccta | acctgaaatc | ccccctctctg | ccctggctgg | atccggggga | cccccttgcc | 1860 |
| cttccctcgg | ctcccagccc | tacagacttg | ctgtgtgacc | tcaggccagt | gtgccgacct | 1920 |
| ctctgggcct | cagttttccc | agctatgaaa | acagctatct | cacaaagttg | tgtgaagcag | 1980 |
| aagagaaaag | ctggaggaag | gccgtgggcc | aatgggagag | ctcttggtat | tattaatatt | 2040 |
| gttgccgctg | ttgtgtgtgt | gttattaatt | aatattcata | ttattttatt | tatacttaca | 2100 |
| taaagatttt | gtaccagtga | aaaaaaaaaa | aaaaaaaaaa | | | 2140 |

<210> 61
 <211> 257
 <212> DNA
 <213> Homo sapiens

| | | | | | | |
|------------|------------|------------|-------------|------------|------------|-----|
| <400> 61 | | | | | | |
| ctgaggggtc | tcttcttggc | catcttctgt | gtcttcccat | ggcttccct | ctgttatgcg | 60 |
| tctttgtcct | gatttcttct | tccttggctg | gtgaggaggc | cgccgggctc | cgggtccaga | 120 |
| agctctggcc | ggctgktgkt | ctgagccatc | tgccggctctg | ctggtttcac | tgctctggaa | 180 |
| tctggagtga | ggkcatgtag | ctgaagggtg | gatgggaggg | acatgttctc | ccgtggcagg | 240 |
| cgcacgttgt | tgagttt | | | | | 257 |

<210> 62
 <211> 684
 <212> DNA
 <213> Homo sapiens

| | | | | | | |
|------------|------------|------------|------------|------------|------------|-----|
| <400> 62 | | | | | | |
| ggcagcagca | gcgtctgtgc | cggctccagg | tgcttgcctc | tgggtgtgtg | agtgggagac | 60 |
| tttgtccct | ggcctcatcc | tagagaggcc | cctgggtgct | agtgtgagg | cctctggggc | 120 |
| tggaaagcct | cagcagaaag | gaggcactac | tgagcaacta | tgcatgtca | ttgtcgggtt | 180 |
| tggggctttc | ggtggttcc | tggtgactgg | gaattgcttg | tgtgcatgtg | ttgggtgcat | 240 |
| gcttccgggt | ctcagctgcc | ccaggcccg | acaggcaacc | ccttcccatc | caaagccatt | 300 |
| ggtggagctt | ctctggaatc | atttgccaaa | agcccaaggc | agaatccaag | ggtccaagac | 360 |
| catttccatg | gagctcatgt | ttttcttttc | tgtaggaa | tttttttaac | cagcaccac | 420 |
| cataattccg | aaggccacgt | ttcatctttc | ctggatcact | acagtgaagt | attacagttg | 480 |
| tacagttccc | agtctggcct | tggtctgctc | ggataaaact | ttgtatgtat | tttgtatggc | 540 |
| atagattcta | tattgtaatg | atgtcctatg | caaaaagaaa | aattaacgaa | attgtaaatt | 600 |
| ttattgtttt | aacgtgtatg | catgtttagt | gacgtttaca | ttttgaaata | aaatttatga | 660 |
| ttcattaaaa | aaaaaaaaaa | aaaa | | | | 684 |

<210> 63
 <211> 1977
 <212> DNA
 <213> Homo sapiens

| | | | | | | |
|------------|------------|-------------|-------------|------------|------------|-----|
| <400> 63 | | | | | | |
| tcgaccacg | cgtccggcaa | ctcaagttca | tcattgtcct | gagagagagg | agcagcgcg | 60 |
| ttctcgccg | ggacagcaga | acgccagggg | accctcacct | gggcgcgcg | gggcacgggc | 120 |
| tttgattgtc | ctggggctgc | ggagaccgc | gcgcctgcc | tgacgcgcg | gcggcaacct | 180 |
| ttgcagtcgc | gttggctgct | gcatcgccg | ggcgggtccc | tgccgaaggc | tcggctgctt | 240 |
| ctgtccacct | cttacacttc | ttcattttatc | ggtggatcat | ttcgagagtc | cgtcttgtaa | 300 |
| atgtttggca | ctttgctact | ttattgcttc | ttcttgccga | cagttccagc | actcgccgag | 360 |
| accggcggg | aaaggcagct | gagcccgagg | aagagcgaaa | tatggggacc | cgggctaaaa | 420 |
| gcagacgtcg | tccttcccg | ccgtattttc | tatattcagg | cagtggatac | atcagggaat | 480 |
| aaattcacat | cttctccagg | cgaaaaggte | ttccagggtga | aagtctcagc | accagaggag | 540 |
| caattcacta | gagttggagt | ccaggtttta | gaccgaaaag | atgggtcctt | catagtaaga | 600 |
| tacagaatgt | atgcaagcta | caaaaatctg | aagggtggaag | ttaaattcca | agggcaacat | 660 |
| gtggccaaat | ccccatatat | tttaaaaggg | ccggtttacc | atgagaactg | tgactgtcct | 720 |

| | | | | | | |
|-------------|-------------|------------|------------|------------|------------|------|
| ctgcaagata | gtgcagcctg | gctacgggag | atgaactgcc | ctgaaaccat | tgctcagatt | 780 |
| cagagagatc | tggcacatth | ccctgctgtg | gatccagaaa | agattgcagt | agaaatccca | 840 |
| aaaagatttg | gacagaggca | gagcctatgt | cactacacct | taaaggataa | caagggttat | 900 |
| atcaagactc | atgggtgaaca | tgtagggttt | agaattttca | tggatgccat | actactttct | 960 |
| ttgactagaa | aggtgaagat | gccagatgtg | gagctctttg | ttaatttggg | agactggcct | 1020 |
| ttggaaaaaa | agaaatccaa | ttcaaacatc | catccgatct | tttcctgggt | tggctccaca | 1080 |
| gattccaagg | atatcgtgat | gcctacgtac | gatttgactg | attctgttct | ggaaaccatg | 1140 |
| ggccgggtaa | gtctggatat | gatgtccgtg | caagctaaca | cgggtcctcc | ctgggaaagc | 1200 |
| aaaaattcca | ctgccgtctg | gagagggcga | gacagccgca | aagagagact | cgagctgggt | 1260 |
| aaactcagta | gaaaacaccc | agaactcata | gacgtctgct | tcaccaactt | tttcttcttt | 1320 |
| aaacacgatg | aaaacctgta | tgggtcccat | gtgaaacata | tttcattttt | tgtatttctt | 1380 |
| aagcataagt | atcaaataaa | tatcgatggc | actgtagcag | cttatcgcc | gccatatttg | 1440 |
| ctagttgggt | acagtgttgt | gctgaagcag | gattccatct | actatgaaca | tttttacaat | 1500 |
| gagctgcagc | cctggaaaca | ctacattcca | gttaagagca | acctgagcga | tctgctagaa | 1560 |
| aaacttaaat | gggcgaaaga | tcacgatgaa | gaggccaaaa | agatagcaaa | agcaggacaa | 1620 |
| gaatttgcaa | gaaataatct | catggggcgt | gacatatctt | gttattattt | caaacttttc | 1680 |
| cagaccaaaag | atgaactctg | atatgcaaaa | taacttctat | tagaataatg | gtgctctgaa | 1740 |
| gactcttctt | aactaaaaag | aagaattttt | ttaagtatta | attccatgga | caatataaaa | 1800 |
| tctgtgtgat | tgtttgcagt | atgaagacac | atttctactt | atgcagtatt | ctcatgactg | 1860 |
| tactttaaag | tacattttta | gaattttata | ataaaacacc | tttattttta | aggaaaaaaa | 1920 |
| aaaaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | aaaaaaa | 1977 |

<210> 64
 <211> 2632
 <212> DNA
 <213> Homo sapiens

| | | | | | | |
|-------------|-------------|-------------|-------------|------------|------------|------|
| <400> 64 | | | | | | |
| ggcagcaggt | gacagagaga | tactctgtct | cttaaaagaa | agaaaaagaa | aaaagagaag | 60 |
| gggatctctg | ggcaagagct | ggaaagtcct | cagacagctc | tgaggtagcc | cctctcatgg | 120 |
| gctccgtgga | ttatctcatg | gcctgtgtgg | ctgtctgtct | ttatctctag | tgacatctct | 180 |
| gcttttctct | gccaagatth | atcccttctc | tgcagccact | tgctgtccag | cttcccttct | 240 |
| ttgtagaatc | tgctctgtcc | caataccttt | actttcgtgt | ggcctctctg | ggctcctcca | 300 |
| tatcatgacc | tgctcagctc | tctttaactc | ctttcttctc | tcaagtgttt | ctcagatcag | 360 |
| agaccagatt | gcaatgagag | aatcagtttg | gtctggtagt | atttcacgcc | aaaaagagtt | 420 |
| ggctaccctt | tggattatat | gcctttgggt | caggcaccta | cccctgggtc | tggctgttgg | 480 |
| ggatggatgg | tgactgttat | gtggccttta | cagggtctta | ggcacaataa | agctttccca | 540 |
| ggttcagcct | actgagtgtc | atggctatga | cctggacatt | aaactggccc | tcataggttc | 600 |
| agacctggcc | atggcaattg | acgaacccta | ccacagggtc | cttggaaacc | tgtgaaagcc | 660 |
| atthttattgt | atgttcttgg | ctgttgaaag | gagttgtagc | ccagctgatg | gcttccattt | 720 |
| cttttctgtg | gatcttgcct | tcatacatag | catgttttag | gggtatagca | tggaaagagg | 780 |
| agatcagggg | ctcagcctgg | ttttcaacta | taggatttag | cagtcagtat | tgggttgctc | 840 |
| agtctggcca | tgacagaatt | ggagccggcc | ctcaggactc | ttgattttta | gctctctgcc | 900 |
| ctttctgttt | acagacccat | ggcacagaaa | gccttatgcc | cagacactgc | aggatgcaga | 960 |
| gttatggagc | catatccttt | cagaggaatg | cctggctact | caacagggtt | ggaaagtcaa | 1020 |
| acaaggatca | acacctactt | ttgcctgctg | tgtgatgggc | ccgagcctgc | aaagctggac | 1080 |
| caaatctggc | cccttttcta | agggcggggg | gcagtcacct | tctagttagg | gaaggaattt | 1140 |
| agctctactt | ctccttttag | aatctggagt | atagacaag | tcaaagcaag | ttaatgaggg | 1200 |
| gttaacataa | cctcagagga | ccactttgag | tctaaagtcc | ttccagatgt | gtcagatttg | 1260 |
| tagcgcaca | ttgtcagttt | ctattaagaa | gtaataggac | tgggtcttct | gggtgtgagg | 1320 |
| gaaagttagt | ctgtgcttaa | atgtccttcc | actctgtcac | aaacaggaga | ttgaaactta | 1380 |
| gggtgcctcca | ttcttatctg | taacctctct | cagggttggt | tttgaggatg | cagttagtta | 1440 |
| atgatgccc | ccagaagcag | gggaagggaa | ctgctttggg | gggactccta | tgtgttacac | 1500 |
| tgaaggatac | cttttaactg | tttatgacgt | tctgttctc | ttgttaactc | gtaaggctcg | 1560 |
| ggttatccct | gctttctaga | tgaagaaaca | ggcttagagc | tatttaggtc | aaggctacaa | 1620 |
| aactggcatg | tgacaacaga | gatttaagta | taattttggaa | gggtggctgt | tccaccacac | 1680 |
| cacaccctac | tggtaggggt | gttgtgatca | catgggtaac | agctgtgaaa | gtcaccaaga | 1740 |
| gcttttctgt | catccagaag | cccttgatct | agaggcacat | cagtctctct | tgctgagaag | 1800 |
| gaggggacac | cactccatgc | tgttgacatc | tcttgagttt | taaaaatggg | cttttacttc | 1860 |
| agggtatact | ctatttaagt | gttcacacat | ggatgaaatt | ctttgtctgt | gactgtgcga | 1920 |
| gataaataaa | aactgtggta | gggcaccagg | ccctgagcta | ggccaggcag | gtttggacaa | 1980 |
| tttctctaag | ctttttataag | gaaaactggg | tttaaaaaaa | aaagttagcc | tgggtacagt | 2040 |
| gattcatgga | ctgggttaggt | tgggtttttt | gggtttgttt | cctcctatcc | tttttttata | 2100 |
| tggaaaaaaa | ttatgcatgc | ttggaaaagga | aaattttgtg | cttttcatth | atcttttact | 2160 |
| tatcacctga | gcctttctct | aggaggcaga | gagtgaatta | aaggctggaa | aagcagtatc | 2220 |
| tgatgaggct | cagttttctg | acagcccacc | agcccttctc | tggaccaagt | acattttcac | 2280 |

| | | | | | | |
|-------------|------------|------------|-------------|-------------|-------------|------|
| tacaaagagg | tgtgactaat | ctttcagagc | aagtgatatt | ttagaagcag | tagttggacc | 2340 |
| agatgtgggtg | gcgcatgcct | gtaatcccag | caactttggga | ggctaaggca | ggaggggtcac | 2400 |
| ttgaggccag | gagtttgaga | ccaacttggg | caacatagca | agaccccatc | tctacaaaaa | 2460 |
| gtaaaaata | aaaattagct | gggcatgttg | acatgtgcct | gtagtccctag | ctactcagga | 2520 |
| ggctgaggtg | gaaggattgc | ttgagcctag | gagtttgagg | ctgcagtgat | caccactgca | 2580 |
| ctacagcctg | ggtgacagag | tgagatcctg | tctcaaaaaa | aaaaaaaaaa | aa | 2632 |

<210> 65

<211> 1241

<212> DNA

<213> Homo sapiens

<400> 65

| | | | | | | |
|-------------|------------|-------------|------------|------------|------------|------|
| ggcacgagtt | cctgcgatga | gaacagagggc | acaggtgccg | gccctgcagc | ccccagaacc | 60 |
| tggactggag | ggggccatgg | ggcaccggac | cctggtcctg | ccctgggtgc | tgctgacctt | 120 |
| gtgtgtcact | gcggggaccc | cggaggtgtg | ggttcaagtt | cggatggagg | ccaccgagct | 180 |
| ctcgtccttc | accatccgtt | gtgggttcct | ggggtctggc | tccatctccc | tggtgactgt | 240 |
| gagctggggg | ggccccgacg | gtgctggggg | gaccacgctg | gctgtgttgc | accagaacg | 300 |
| tggcatccgg | caatggggcc | ctgctcgcca | ggcccgtgg | gaaaccaga | gcagcatctc | 360 |
| tctcatcctg | gaaggctctg | gggccagcag | cccctgcgcc | aacaccacct | tctgctgcaa | 420 |
| gttttgcgtcc | ttccctgagg | gctcctggga | ggcctgtggg | agcctcccgc | ccagctcaga | 480 |
| cccagggctc | tctgccccgc | cgactcctgc | ccccattctg | cgggcagacc | tggccgggat | 540 |
| cttgggggtc | tcaggagtcc | tcctcttttg | ctgtgtctac | ctccttcate | tgctgcgccg | 600 |
| acataagcac | cgccctgccc | ctaggctcca | gccgtcccgc | accagccccc | aggcaccgag | 660 |
| agcacgagca | tgggcaccaa | gccaggcctc | ccaggctgct | cttcacgtcc | cttatgccac | 720 |
| tatcaacacc | agctgccgcc | cagctacttt | ggacacagct | caccccatg | gggggccgtc | 780 |
| ctggtggggc | tactcccca | cccacgctgc | acaccggccc | cagggccctg | ccgcctgggc | 840 |
| ctccacaccc | atccctgcac | gtggcagctt | tgtctctgtt | gagaatggac | tctacgtca | 900 |
| ggcaggggag | aggcctcctc | acactggtcc | cggcctcact | cttttcctg | accctcgggg | 960 |
| gcccagggcc | atggaaggac | ccttaggagt | tcgatgagag | agaccatgag | gccactgggc | 1020 |
| tttccccctc | ccaggcctcc | tgggtgtcat | ccccttactt | taattcttgg | gcctccaata | 1080 |
| agtgtcccat | aggtgtcttg | ccaggcccac | ctgctgcgga | tgtggtctgt | gtgctgtgt | 1140 |
| gggcacaggt | gtgagtgtgt | gagtgacagt | tacccattt | cagtcatttc | ctgctgcaac | 1200 |
| taagtcagca | acacagtttc | tctgaaaaaa | aaaaaaaaaa | a | | 1241 |

<210> 66

<211> 1154

<212> DNA

<213> Homo sapiens

<400> 66

| | | | | | | |
|------------|------------|------------|------------|-------------|-------------|------|
| ggagactcta | gatccagacc | cacatggcac | ggggctgcct | ccctcaggca | gttctcagcc | 60 |
| aggccccac | ccagggcaca | ggctcaggct | gagcggggtg | gtggatgggc | tggagccggg | 120 |
| gagaagggca | gcaaggctgg | ctggccgcag | ccctctgtgg | ctggacacga | cttggcaagg | 180 |
| ccgagggatc | tgagggtctg | gctactctcg | agggctgcc | ggttcccagc | ttgctgcagg | 240 |
| gaaatgaagg | gggtgccgcc | ctgaacaggc | acatgcctaa | gcaaggattt | gacgcttgga | 300 |
| taaagctggc | aaccaccagg | agaagccttt | ttgggatttt | tcaaattcctt | cgctcatccga | 360 |
| gctgtgatga | tggagtggag | cgtggcacgg | gcccatggga | gttctgtggg | ctccatcggc | 420 |
| actcagcagg | gatttggacg | tgcaggctgg | tgggccctgc | aggaagcctg | ctccctgtctc | 480 |
| tgctgcgtgg | gagggggcag | ctcgggggaa | gggsccttgc | agagaaacag | agaacatgg | 540 |
| gctgtggggc | accttcagca | gcccgggggt | ccaatcccag | ctcctccatg | tgggagccaa | 600 |
| gcaccccagg | cagccttttc | cagccttgct | tagggccggg | ttgggagaat | cccaccccgc | 660 |
| agggctgttg | tgagggttga | acggaggggt | tgtgtgtagg | gttgagcgga | gggtgtgtga | 720 |
| tgcgtgggtg | gggttgagca | ataagaaacc | agaaccttgc | agcctccagg | gcccgggtgc | 780 |
| gtttgcaggc | cagtgccac | tgtccgggct | gtgatggcac | caaggcaggt | ggagcaccag | 840 |
| gtaccacaca | gctgggcttc | ccaccaggct | ttcccgcggg | ggtctcaggg | agcttctccc | 900 |
| cagcgtgct | cggagtctgc | aggaactggc | cttgttctcc | ttagcccgtc | actccataca | 960 |
| gtattaggtg | aggatggatg | cgggcgctgt | ccttgccggg | aagtcactgt | tgaagttgca | 1020 |
| gtggcttgtt | cacacctgtg | ggaagagaag | tgaagacttt | ctccttgcat | taaaaagtct | 1080 |
| gaactgtgaa | aaaaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | aaaaaaaaag | aggttctaga | 1140 |
| tcgcgagcgg | ccgc | | | | | 1154 |

<210> 67

<211> 1077

<212> DNA

<213> Homo sapiens

<400> 67

| | | | | | | |
|-------------|-------------|-------------|-------------|------------|------------|------|
| ggcagcagga | gaacagctga | cgggtctttcc | ataagtgcctt | ctaagagaga | tgtgtggtac | 60 |
| cccgggctaa | gtagacagca | actgagccct | ccctcccacc | ccagggctcc | cagagcaaca | 120 |
| gggagcaggg | agcataggac | ctggccgcag | ccaggaatct | acactgaccg | gctcagccca | 180 |
| tgaagtatct | tgggctgaag | tcacaggatg | agactgtttg | tatctgtaac | tgtccttgct | 240 |
| atctgtcttg | cagatttaga | agaggaatca | gaaagctggg | acaactctga | gtctgaagag | 300 |
| gaggagaaa | cccctgtgtt | gccagagagt | acagaagggc | gggagctgac | ccagggcccc | 360 |
| gcagagtcct | cctctctctc | aggctgtggg | agctggcagc | cccggaagct | gccagtcctc | 420 |
| aagtcctctc | ggcacatgag | gcaggtaggc | ggcaggggca | cagcgcacat | ggagctcagg | 480 |
| aggagagcca | atcatgggct | gtccctgccc | acacgccttg | cctctggacc | ctccaccttc | 540 |
| aaaaccctgc | aggaagtgac | tgacagcctc | ctcgggtgggt | ggctgagggc | acagggcggt | 600 |
| gggggtatta | gccataggat | cagtgtctcc | ctttcagtga | tgacctaaat | atcttcaaa | 660 |
| aaaagcccag | atagttggca | tcccatgggc | ctctaactct | ctaagaagct | cctaaaggca | 720 |
| ttgaacagca | ctgtaattgg | tttggatgca | gcctggaccc | tgcccatgtt | aagtgatggg | 780 |
| ctggctgggc | gtgggtggctc | tcacctgtaa | tcccagcact | ttgggaggcc | aagggggagc | 840 |
| ggatcacagag | gtcaggagtt | cgagaccagc | ctggccaaca | tggtgaaacc | ccatctctat | 900 |
| taatacaaaa | attagctggg | catgggtggc | tgtgcctgta | gtcccagcta | cttggaggct | 960 |
| gaggcaggag | aatcgcttga | acctgggagg | tggagggttaa | cagtgaacca | agatggcacc | 1020 |
| actgcactcc | agactggtga | cagagcgaga | ctccatctca | aaaaaaaaaa | aaaaaaa | 1077 |

<210> 68

<211> 3067

<212> DNA

<213> Homo sapiens

<400> 68

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| ccacgcgtcc | gattatatta | gtcttggtc | ttttagaaac | tagtttgctt | catcactttg | 60 |
| ctggcttctc | acagatttct | aaaagcaatt | cccaggctat | tgtgggctat | ggtttgatga | 120 |
| tattacttat | aatactgtgg | atacttagag | aaattcaaa | catatatatc | attggaattt | 180 |
| tccgaaatcc | cttttatccg | aaggatgtgc | aaactgtgac | tgtattcttt | gagaagcaaa | 240 |
| ctaggctcat | gaagattggg | attgtcagac | ggattttgct | aactttagta | tcaccttttg | 300 |
| ccatgatagc | atttctttca | ttggacagtt | ccttacaagg | gctccactca | gtgtctgtct | 360 |
| gtattggatt | cacaagagcc | tttagaatgg | tatggcagaa | tacagaaaat | gctttatttg | 420 |
| agacagtcat | tgtatcaaca | gtacacttga | tctccagtac | agacatatgg | tggaacagaa | 480 |
| gcctggatag | aggactcaga | ctcttactgg | ttggttatcat | acgtgatcgt | ttgattcagt | 540 |
| tcctctctaa | attgcagttt | gccgtgactg | tgtttttgac | atcatggaca | gagaaaaaac | 600 |
| aacgtcgaaa | aacaactgcc | actttatgta | tactcaacat | tgtcttttct | ccattcgtgt | 660 |
| tggtcatcat | agttttttct | acactactct | cttctccctt | actccctctt | ttcacccttc | 720 |
| ctgtgttctt | gggtggggtt | ccccgacctt | ttcagagtgt | gccaggagca | gcaggcacca | 780 |
| cagcctgtgt | gtgtgcagat | acagtgtact | actaccaa | gggtgcccagg | ttgactgtct | 840 |
| tactgcagac | tgaattggca | gctggaagtt | taggttctct | cctacctgga | tctcattact | 900 |
| tgggctgggt | tcaggatcgt | ttaatgtgga | taattgattct | ggaatgtggc | tatacttact | 960 |
| gctctattaa | cattaagggg | ttagaattgc | aggaaacatc | ctgtcatact | gcagaagctc | 1020 |
| gcagagttga | tgaagttttt | gaagatgctt | ttgagcaaga | atacacaaga | gtatgttccc | 1080 |
| ttaatgaaca | ctttggaaat | gtcttgacac | cctgtactgt | tttgctgtg | aaattgtatt | 1140 |
| ctgatgccag | gaattgttca | tcaggcataa | ttgatttctca | tgaaaactta | aaagatttta | 1200 |
| aaggtgacct | cattaaagta | cttgtgtgga | tactgttctca | atactgctcc | aaaaggcctg | 1260 |
| gcatgaaaga | gaatgttcac | aacactgaaa | ataaagggaa | agcacctcta | atgttgcttg | 1320 |
| ctttgaacac | tttgccacct | cccaaattcc | cagaagacat | agacagttta | aattcagaaa | 1380 |
| cttttaata | ctggcttgat | gataatat | ttgatgatga | gccaactatc | aaaaaagtaa | 1440 |
| tagaagaaaa | acatcagttg | aaagatttgc | caggtacaaa | tttgtttatt | ccaggatcag | 1500 |
| tagaatcaca | gagggttggg | gatcatttca | caggcactgt | tcttgaaaac | gatctttaca | 1560 |
| aagcagttct | attagatata | cctgtgtgtg | acaaaggaaa | acaagaggac | atgccatata | 1620 |
| ttcctctcat | ggagttcagt | tgttcacatt | ctcacttagt | atgcttacct | gcagagtggg | 1680 |
| ggactagctg | tatgcccagt | tccaaaatga | aggagatgag | ctcgttattt | ccagaagact | 1740 |
| ggtaccaatt | tgttctaagg | cagtttgaat | gttatcatte | agaagagaag | gcctcaaatt | 1800 |
| tactggaaga | aattgccaa | gacaaagttt | taaaagactt | ttatgttcat | acagtaattga | 1860 |
| cttgttattt | tagtttattt | ggaatagaca | atatggctcc | tagtcctggg | catatattga | 1920 |
| gagttttacg | tgggtttttg | ccttggtctg | ttgcttttga | ctgggtcaca | gaaaagccag | 1980 |
| aactgtttca | actagcactg | aaagcattca | ggtatactct | gaaactaatg | attgataaag | 2040 |
| caagtttagg | tccaatagaa | gacttttagag | aactgattaa | gtaccttgaa | gaatatgaac | 2100 |
| gtgactggta | cattgggttg | gtatctgatg | aaaagtggaa | ggaagcaatt | ttacaagaaa | 2160 |
| agccatactt | gttttctctg | gggtatgatt | ctaatatggg | aatttacact | gggagagtgc | 2220 |
| ttagccttca | agaattattg | atccaagtgg | gaaagttaaa | tcttgaagct | gttagaggct | 2280 |
| agtgggccaa | tctttcatgg | gaattacttt | atgccacaaa | cgatgatgaa | gaacgttata | 2340 |

| | | | | | | |
|------------|-------------|------------|-------------|-------------|------------|------|
| gtatacaagc | tcattccacta | cttttaagaa | atctttacggt | acaagcagca | gaacctcccc | 2400 |
| tgggatatcc | gattttattct | tcaaaacctc | tccacataca | tttgtattag | agctcatttt | 2460 |
| gactgtaatg | tcattcaaatg | caatgttttt | attttttcat | cctaaaaaag | taactgtgat | 2520 |
| tcttgtaact | tgaggacttc | tccacacccc | cattcagatg | cctgagaaca | gctaagctcc | 2580 |
| gtaaagtgg | ttctcttagc | catcttaatg | gttctaataa | acagcaaaaa | catctttatg | 2640 |
| tctaagataa | aagaactatt | tggccaatat | ttgtgccctc | tggacttttag | taggctttgg | 2700 |
| taaatgtgag | aaaacttttg | tagaattatc | atataatgaa | ttttgtaatg | ctttcttaaa | 2760 |
| tgtgttatag | gtgaattgcc | atacaaagtt | aacagctatg | taattttttac | atacttaaga | 2820 |
| gataaacata | tcagtgttct | aagtagtgat | aatggatcct | gttgaagggt | aacataatgt | 2880 |
| gtatatatct | gtttgaaata | taattttatg | tatttttcaa | tgtgctgatt | tattttgaca | 2940 |
| tctaataatc | gaatgttttt | gtatcaagta | gtttgttttc | atagacttca | attcataaac | 3000 |
| tttaaaaaac | ttttaataaa | atatttttct | tccttaaaaa | aaaaaaaaaa | aaaaaaaaaa | 3060 |
| aaaaaaa | | | | | | 3067 |

<210> 69
 <211> 3453
 <212> DNA
 <213> Homo sapiens

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| tgtacctttc | ccgaccgggc | cactggaagt | tggagcctcc | gccgagtcgc | agacaacgcc | 120 |
| tccgggaggg | ccttcctgat | gcgcttgctc | gtcctctggg | ctctctgcat | ggggaaggag | 180 |
| tgttcccagc | ttgcaaacct | cagctttgct | tgtgagagga | acaagcgtcc | ctgatccaga | 240 |
| agggtgttcg | atggagatgg | cgagtctctg | tggctcctgg | ctctctgggt | gcctcatccc | 300 |
| tctcgtcttc | ctccggctgt | ctgtgcatgt | gtcaggccac | gcaggggatg | ccggcaagtt | 360 |
| ccacgtggcc | ctactagggg | gcacagccga | gctgctctgc | cctctctccc | tctggcccgg | 420 |
| gacggtaccc | aaggaggtga | ggtggctgcg | gtccccattc | ccgcagcgct | cccaggctgt | 480 |
| tcacatatct | cgggatggga | aggaccagga | tgaagatctg | atgccggaat | ataaggggag | 540 |
| cacggtgcta | gtgagagatg | cccaagaggg | aagtgtcact | ctgcagatcc | ttgacgtgcg | 600 |
| gacttgaggac | caagggtcct | accgatgtct | gatccaagtt | ggaaatctga | gtaaagagga | 660 |
| caccgtgatc | ctgcagggtg | cagcccccac | tgtggggagt | ctctccccct | cagcagtggt | 720 |
| tctggctgtg | atcctgcctg | tcctggtaact | tctcatcatg | gtgtgccttt | gccttatctg | 780 |
| gaagcaaaaga | agagcaaaaag | aaaagcttct | ctatgaacat | gtgacggaga | caatcttctt | 840 |
| tcagaccatg | ctaaagaaaa | aggaaaactc | cataaagctg | tcaagaaact | ccggagtga | 900 |
| ctgaagtgtg | aaagagctgc | agcaaaactc | ggctggagaa | gagcccggtt | gcattttgtg | 960 |
| gcagtgaccc | tggaccacaga | cacagcacat | cccaaaactc | tcctttctga | ggaccaaaaga | 1020 |
| tgtgtaaggc | ttggagacag | acggcagcct | gtacctgaca | acccccagag | atttgatttc | 1080 |
| gttgtcagca | tcctaggctc | tgagtacttc | acgactgggt | gccactactg | ggaggtgtat | 1140 |
| gtgggagaca | agaccaaatg | gattctttga | gtatgtagtg | agtcagtgag | caggaagggg | 1200 |
| aaggttactg | cctcacctgc | caatggacac | tggcttctgc | gacagagtcg | tgggaatgag | 1260 |
| tatgaagctc | tcacatcccc | gcagacctcc | ttccgcctta | aagagcctcc | acggtgtgtg | 1320 |
| gggattttcc | tggactatga | agcaggagtc | atctctttct | acaatgtgac | caacaagtcc | 1380 |
| cacatcttta | ctttcaccca | caatttctct | ggcccccttc | gccctttctt | tgaaccttgc | 1440 |
| cttcatgatg | gaggaaaaaa | cacagcacct | ctagtcatct | gttcagaact | acacaaatca | 1500 |
| gaggaatcaa | ttgtccccag | gccagaaggg | aaaggccatg | ctaattggaga | tgtgtccctc | 1560 |
| aagggtcaact | cttcttttact | acccccgaag | gccccagagc | tgaaggatat | aatcctgtcc | 1620 |
| ttgcccactg | accttggccc | agcccttcag | gagctcaagg | ctccttcttt | ttagggatat | 1680 |
| gccacattac | ctgtctccat | caccatccag | ccagcaccc | tggacttcag | tcgcctggcc | 1740 |
| caaccccatg | attatggaac | gtctcttcac | cttaacccaa | atccagaccc | ttttgtgggt | 1800 |
| tctattttgta | ccacttttct | cccaggcctc | agttctgaag | cttacctttc | ttctaaggaa | 1860 |
| ttgaagctcc | cagtgcctg | gagggaggat | tcctggaaac | caaacaatca | gttttaggtg | 1920 |
| agggtggagat | gttgaatatg | tgttaccaag | atacagcaca | ggttcaggga | aaagagttcg | 1980 |
| ctactccagg | ggttattttag | aagacacttt | ctctgcctca | tcctgccctc | aagcttttagt | 2040 |
| caagaagtta | tggccccag | tcctgacttt | cttactttat | ccatttgagga | ctgcctttct | 2100 |
| ctctctcagt | tctggcctct | gccccccaaa | gtcagctctc | taaaagcaag | catgttttag | 2160 |
| accactcact | ctttccctct | ttcttcagga | atgaattggg | aaaggctgat | gagtaaaaca | 2220 |
| taccatcctt | ttctattttc | ttgatgctgt | ttacaacata | gtttggtgat | atccagagct | 2280 |
| aatgtacatg | ctttcaaaaag | ctaactctgc | tgttgatgat | aactaggtac | agcgacttta | 2340 |
| aatacagttg | ctataatcct | gaaaagcccc | aggagcacat | cagggagctg | ggaaacacag | 2400 |
| ttgcagagtaa | ctcagctgta | tgttgccctc | tgaccttggc | ccagaccttc | agaggctcag | 2460 |
| tctgttgagt | ctgttgtgac | tgtcttatga | atcaatctgt | tgtgcccaacc | ctttctgaga | 2520 |
| ttcagagagg | tccagctaga | aaaagtggca | gttttaacca | ccaacgtaga | agcttttttt | 2580 |
| ttccccacaa | gaccattgta | ctgcaatact | tgactatttg | tgtagcaaac | agcctcttag | 2640 |
| gttgagaggt | attgattttca | aataggaagt | tggtagacta | ggtgtgagga | tgaataaatg | 2700 |
| accttgattt | ttgggtgtgt | attgcagaag | cctcgtcgtc | ttcaagtcac | atcatatatg | 2760 |

| | | | | | | |
|------------|------------|-------------|-------------|-------------|-------------|------|
| cgatctggcc | taaccatgga | gatattgggt | atcagtttgc | agatgaatac | acagttctat | 2820 |
| ccaacagaaa | ctgtatcttt | ctgtttgtca | gaagttctcc | gttagttcct | gtattagtca | 2880 |
| agggtttcca | gagaaacaga | atcaatatat | attggggcag | gggggcgggtg | gttattataa | 2940 |
| ggaattggct | cacgtgatta | tggaggcgggt | taaattccaa | gatctgcagg | ataagtcagc | 3000 |
| aagatggagt | cccatgagag | ctgatgggtt | agttccagtc | tgatggcagc | aggcttgacg | 3060 |
| ccaaggaaga | gatgatgttt | aattcaagtc | cgaaggcaag | gaaaaagctg | atggctcctgt | 3120 |
| ccaaaggcta | ttaggcagga | agaattctct | tagggcagag | ttagctcttt | tgttctattc | 3180 |
| aggccttcaa | ctgattcagc | aaggcccgcc | cacatttggg | aggacagtct | gcattactca | 3240 |
| gtctactgat | ttgaatgtta | atgtcattga | gaaacaccct | cacaggaaca | ctcagaataa | 3300 |
| tgtttgacca | aatagctggg | catcttgtga | cccagtttaag | tggatacata | agattaacta | 3360 |
| tcacagtgc | tcagtggaa | tttttgtttg | cttttgtaca | gttttaaaat | aaaagtttgg | 3420 |
| tatttgtgtt | ttggaaaaaa | aaaaaaaaaa | aaa | | | 3453 |

<210> 70
 <211> 1109
 <212> DNA
 <213> Homo sapiens

| | | | | | | |
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| <400> 70 | | | | | | |
| ccacgcgtcc | gcgagcgcgt | gggtcgccca | cgcgtccgtg | tttccattag | tgatactgat | 60 |
| gtctcactgt | tgttctctcc | gagttgactt | ttctgtgcct | ttgtgcatgc | tcttatctcc | 120 |
| tctgcttgga | atgtcctttt | cagcctgtca | aactccttca | aaatccagct | cagatgttac | 180 |
| attttcttta | agcactcctg | accccccccc | ccaaatagac | ttagtccagc | cttcttctgg | 240 |
| gttcccacag | cactcagtag | agtttgaaag | gtcctttata | atagtcatta | ttacattttt | 300 |
| caaaaataat | ttcatattca | ttaacctcat | tagattataa | gcacctcaat | tatgtagact | 360 |
| gttttatcac | tgctgtccca | gcacagcacc | tggcacagtt | agctgttcaa | gacatctctg | 420 |
| ttgagtgggt | aaatgaatga | gttccactcc | aggttcctgt | gtttgtgacc | tccaggggcc | 480 |
| tcttctcttc | ccttccccct | ctcacgtagg | ctgatgccct | ggctctccag | ctatgcactc | 540 |
| tacctgcctc | tcgatgctct | aagccgatgt | gtccatcatt | tggctgtttg | catattctga | 600 |
| ttcatgacat | tttctgcac | agtgtcggct | gacactctgt | agccccatcat | atctgacttc | 660 |
| tctggccagc | ctgtatgcct | accatcagct | cgccctccaa | ggcacagtcc | ttccccgttt | 720 |
| cctgatgttt | tcaattctgc | cccagccatg | caaattctcag | cacacacagc | tcattaaata | 780 |
| gctttgaacc | tctcccttct | ttttttttca | atactgtttg | gcaaattgctt | tccaagagcc | 840 |
| tactaagggc | tgggcacagc | gcctcatgcc | tgtaatccca | gcactttggg | aggccgaggg | 900 |
| agttagatca | cctgaggtca | gaggttggag | accagcctgg | ccaacatggg | gaaaccacat | 960 |
| ctctactaaa | aatacaaaaa | ttagctgggt | gtgggtggcag | gcacctgtaa | tctcagctac | 1020 |
| ttgggagggt | gaggcaggag | agtcgcttga | accgggcact | ccagcctggg | tgacaagagc | 1080 |
| aaaactcctt | ctcaaaaaaa | aaaaaaaaaa | | | | 1109 |

<210> 71
 <211> 1158
 <212> DNA
 <213> Homo sapiens

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| gtggtggcga | ggcttgcaga | aactccagtt | ccaacctcca | ggctgtgtga | ttgtcctgtc | 120 |
| cctggggctg | gtctaaatgc | tccattcatt | ggcattggct | gagttctgcc | gggattggga | 180 |
| gcactgcggt | ccggcttgta | gtcccacagt | tgctgtgctc | tttccccgtg | tgcagcgcag | 240 |
| attcttcttc | tgtgccctgt | ggttgctacg | agcgcagggg | ggagggctgg | ggtcagcaat | 300 |
| tcaagactgt | cttttctatc | ctcttcactg | cctctttcag | caatatgaag | gtactgtgat | 360 |
| tgctcacatg | atttttgggt | cttatgaagg | tgctttttgt | gtaggtgggt | gtcagatttg | 420 |
| gtgttcctgc | agggaggaca | atcgggtggg | gcttctattt | ggccatattg | ctctgcctcc | 480 |
| cattccagct | tgtttctatt | tttaattttt | gttgcaatgg | agtcttttgc | ctggccctga | 540 |
| ataatattta | aataaatcac | aaggacttga | aactacaaaa | tgtatactta | gagccaaagt | 600 |
| caccttactt | gtaagaactg | gaaatgggga | taatgctctc | tatggttatg | cagcctactc | 660 |
| ttttactaac | ctttctggac | tagatctttg | aagtgcgtct | tagctttcct | cctttcctga | 720 |
| agagagcaga | gatagtgtctg | ctttaactgt | ggtcatacat | gtatgaggaa | taactttagt | 780 |
| gtgagctgtt | ggtttttaag | agtcataat | tattctatgc | acttttgtaa | gttcatttta | 840 |
| taatgagcag | attggccaac | tgacattttt | gattatttgt | aatacatgtg | ttgcttggaa | 900 |
| taatactgtt | aatttccaga | aactttagct | tttctgttgg | tggcttttta | | 960 |
| actttttatg | atgggaaaaa | gtgtgaattt | tctcctggga | aagtatagac | tggagactta | 1020 |
| gataccagta | gatgaattga | ggaatttctg | tgtagcagtt | taatatagaa | aagagttagc | 1080 |
| tgtccatgag | gaagggcttt | aagaacaaca | ataactacca | aaaaaaaaaa | aaaaaaaaaa | 1140 |
| aaaaaaaaaa | aaaaaaaaaa | | | | | 1158 |

<210> 72
 <211> 1269
 <212> DNA
 <213> Homo sapiens

<400> 72
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 gacacaagtt cagcccagag ccggggctat gggggccagc gggcacctgg tggcctgagt 180
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 gccccgcccc caaccaagg tgctgagaga tctccagctg cacaggccac cgccccaggg 1140
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<210> 73
 <211> 2911
 <212> DNA
 <213> Homo sapiens

<400> 73
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 acgagaatga agccatccaa tggatgcagg aaaactggaa gaaatctttc ctgttttctg 240
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| | | | | | | |
|-------------|------------|-------------|------------|-------------|------------|------|
| actgtgagct | ggaaaagggg | gaaaggcagt | gggaaaagag | gtgagccgaa | gatcaattcg | 1920 |
| acagacagac | ggtgtgtatg | cccctccctg | tttgacttca | cacacactca | taactttcca | 1980 |
| aatgaaaccc | cacagtatag | cgcataatgtt | cgataatgtt | gtgaattcca | aaaggaaatc | 2040 |
| acagggctgt | tcgaaatatt | gggggaacac | tgtgtttctg | catcatctgc | atttgctccc | 2100 |
| caagcaatgt | agaggtgttt | aaagggccct | ctgctggctg | agtggcaata | ctacaacaaa | 2160 |
| cttcaaggga | agtttggctg | aaaacagttg | acaacaaagg | gccccatac | acttatccct | 2220 |
| caaattttta | gtgatatgaa | atacttgtca | tgtctttggc | ccaatcagaa | gatattcatc | 2280 |
| ctgcttcaag | tcagcttcag | aaatgtttta | aaagggactt | tagctctgga | actcaaaatc | 2340 |
| aattttattaa | gagccatatt | ctttaaaaaa | aaaaagctgg | ataatattat | ctgtaatatt | 2400 |
| tcagtccttt | acaagccaaa | tacatgtgtc | aatgtttcta | gtatttcaaa | gaagcaatta | 2460 |
| tgtaaagttg | ttcaatgtga | cataatagta | ttataatttg | ttaagtagct | taatgattag | 2520 |
| gcaaactaga | tgaagaagtt | aggggcttcc | acactgcata | gattacacgc | acatagccac | 2580 |
| gcatacacac | acagacacac | agatgtgggg | tacactgaac | ttcaaagccc | aaatgaatag | 2640 |
| aaacacattt | tctggctagc | agaaaaaac | aaaacaaaac | tgttgtttct | ctttcttgct | 2700 |
| ttgagagtgt | acagtaaaag | ggattttttc | gaattatttt | tatattattt | tagctttaat | 2760 |
| tgtgctgtcg | ttcatgaaac | agaactgtct | tgtttttctg | tcagagatgg | caagggtctt | 2820 |
| ttcagcatct | cgtttatgtg | tggaaatttaa | aaagaataaa | gtttttattcc | cttctgtggt | 2880 |
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<210> 74
 <211> 5023
 <212> DNA
 <213> Homo sapiens

| | | | | | | |
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| ggtccccagg | cgtctggagg | gagcccagca | tccatcacgc | cacagctgcc | tctggcccc | 120 |
| aggagcctgc | aggtggggac | tcctccgtgg | ccacacaaaa | caacgatggc | actgacgggc | 180 |
| aaaagctgct | tttattctac | atcctaggca | ccgtgggtggc | catcctactc | ctgctggccc | 240 |
| tggctctggg | gctactggtc | tatcgcaagc | ggagagcgaa | gagggaggag | aagaaggaga | 300 |
| agaagcccca | gaatgcggca | gacagttact | cctgggttcc | agagcgagct | gagagcaggg | 360 |
| ccatggagaa | ccagtacagt | ccgacacctg | ggacagactg | ctgaaagtga | ggtggcccta | 420 |
| gagacactag | agtcaccagc | caccatyctc | agagctttga | actccccatt | ccaaaggggc | 480 |
| acccacattt | ttttgaaaga | ctggactgga | atcttagcaa | acaattgtaa | gtctcctcct | 540 |
| taaaggcccc | ttggaacatg | caggtatttt | ctacgggtgt | ttgatgttcc | tgaagtggaa | 600 |
| gctgtgtgtt | ggcgtgccac | ggtgggggatt | tcgtgactct | ataatgattg | ttactcccc | 660 |
| tcctttttca | aattccaatg | tgaccaattc | cggatcaggg | tgtgaggagg | ctggggctaa | 720 |
| ggggctcccc | tgaatatctt | ctctgctcac | ttccaccatc | taagaggaaa | aggtgagttg | 780 |
| ctcatgctga | ttaggattga | aatgatttgt | ttctcttcc | aggatgaaaa | ctaaatcaat | 840 |
| taattattca | attaggtaag | aagatctgg | tttttggta | aagggaacat | gttcggactg | 900 |
| gaaacatttc | tttactttg | cattcctcca | tttcgccagc | acaagtcttg | ctaaatgtga | 960 |
| tactgttgac | atcctccaga | atggccagaa | gtgcacattaa | cctcttaggt | ggcaaggagg | 1020 |
| caggaagtgc | ctcttttagt | cttacatttc | taatagcctt | gggtttattt | gcaaagggaag | 1080 |
| cttgaaaaat | atgagaaaag | ttgcttgaag | tgcattacag | gtgtttgtga | agtcacataa | 1140 |
| tctacggggc | tagggcgaga | gaggccaggg | atttggtcac | agatacttga | attaattcat | 1200 |
| ccaaatgtac | tgaggttacc | acacacttga | ctacggatgt | gatcaacact | aacaaggaaa | 1260 |
| caaattccaag | gacaacctgt | ctttgagcca | gggcaggcct | cagacaccct | gcctgtggcc | 1320 |
| ccgcctccac | ttcatcctgc | ccggaatgcc | agtgctccga | gctcagacag | aggaaggcct | 1380 |
| gcagaaaagt | ccatcaggct | gtttcctaaa | ggatgtgtga | acgggagatg | atgcactgtg | 1440 |
| ttttgaaagt | tgtcatttta | aagcatttta | gcacagttca | tagtccacag | ttgatgcagc | 1500 |
| atcctgagat | tttaaactct | gaagtgtggg | tggcgcacac | accaagtagg | gagctagtca | 1560 |
| ggcagtttgc | ttaaggaaact | tttgttctct | gtctcttttc | cttaaaattg | ggggtaagga | 1620 |
| gggaagggaag | agggaaagag | atgactaact | awaatcattt | ttacagcaaa | aactgctcaa | 1680 |
| agccattttaa | atttatctct | cattttaaaa | gttacatttg | caaataattc | tccttatgat | 1740 |
| aatgtagtgc | atagtgtgca | ctctttctct | ctctctctct | ctctcacaca | cacacacaca | 1800 |
| cacacacaca | cacacacaca | sacacggcac | cattctgcct | ggggcactgg | aacacatttc | 1860 |
| tgggggtcac | cgatggtcag | agtcactagr | agttacctga | gtatctctgg | gaggectcat | 1920 |
| gtctcctgtg | ggctttttac | caccactgtg | caggagaaca | gacagaggaa | atgtgtctcc | 1980 |
| ctccaaggcc | ccaaagcctc | agagaarggg | tgtttctggt | tttgcttag | caatgcactg | 2040 |
| gtctctgagg | gagcactctg | gagcggttga | agggccacaa | ggtgcagggt | taatactctt | 2100 |
| gccagttttg | aaatatagat | gctatggttc | agattgtttt | taatagaaaa | ctaaaggggc | 2160 |
| aggggaagtg | aaaggaaaga | tggaggtttt | gtgcggctcg | atggggcatt | tggaaacttct | 2220 |
| ttttaaagtc | atctcatggg | ctccagtttt | cagttggaac | tctgggtgtt | aacacttaag | 2280 |
| ggagacaaaag | gctgtgtcca | tttggcaaaa | cttccttggc | cacgagactc | taggtgatgt | 2340 |
| gtgaagctgg | gcagtctgtg | gtgtggagag | cagccatctg | tctggccatt | cagaggattc | 2400 |
| taaagacatg | gctggatgcg | ctgctgacca | acatcagcac | ttaaataaat | gcaaatgcaa | 2460 |

| | | | | | | |
|-------------|-------------|------------|-------------|-------------|-------------|------|
| cattttctccc | tctgggcctt | gaaaatcctt | gcccttatca | tttgggggtga | aggagacatt | 2520 |
| tctgtccttg | gcttcccaca | gccccaacgc | agtctgtgta | tgattcctgg | gatccaacga | 2580 |
| gccctcctat | tttcacagtg | ttctgattgc | tctcacagcc | caggcccatc | gtctgttctc | 2640 |
| tgaatgcagc | cctgtttctca | acaacaggga | ggatcatggaa | ccccctctgtg | gaaccacaaa | 2700 |
| ggggagaaat | gggtgataaa | gaatccagtt | cctcaaaacc | ttccctggca | ggctgggtcc | 2760 |
| ctctcctagct | gggtgggtgct | ttctcttgca | caccactccc | accacggggg | gagagccagc | 2820 |
| aacccaacca | gacagctcag | gttgtgcata | tgatggaaac | cactgggctc | aaacacgtgc | 2880 |
| tttattctcc | tgtttatttt | tgctgttact | ttgaagcatg | gaaattcttg | tttgggggat | 2940 |
| cttggggcta | cagtagtggtg | taaacaaatg | cccaccggcc | aagaggccat | taacaaatcg | 3000 |
| tccttgtcct | gagggggcccc | agcttgtctg | ggcgtggcac | agtgggggaat | ccaagggtca | 3060 |
| cagtagtggtg | agaggtgcac | cctgccacct | gctaacttct | cgtagacac | agtgtttctg | 3120 |
| cccaggtgac | ctgttcagca | gcagaacaag | ccagggccat | ggggacgggg | gaagttttca | 3180 |
| cttggagatg | gacaccaaga | caatgaagat | ttgttgtcca | aatagggtcaa | taattcttggg | 3240 |
| agactcttgg | aaaaaactga | atatattcag | gaccaactct | ctccctcccc | tcaccccaca | 3300 |
| tctcaaagca | gacaatgtaa | agagagaaca | tctcacacac | ccagctcgcc | atgcctactc | 3360 |
| attcctgaat | ttcaggtgcc | atcactgtct | tttcttttctt | ctttgtcatt | tgagaaagga | 3420 |
| tgcaggagga | caattcccac | agataatctg | aggaatgcag | aaaaaccagg | gcaggacagt | 3480 |
| tatcgacaat | gcattagaac | ttgggtagca | tcctctgtag | agggactcca | cccctgtctca | 3540 |
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| cctaagcgct | atcgctcattg | ccatagcatc | atgatgcaac | acatctacgt | gtagcactac | 3660 |
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| tggtggagga | gcaaggcttc | aggaaggggc | agccacatgc | catcttcctt | gcgatcaggc | 3840 |
| aaaaaagtgg | aattaaaaag | tcaaaccctt | atatgcattg | gttatgtcca | ttttgcagga | 3900 |
| tgaactgagt | ttaaaagaat | ttttttttct | cttcaagttg | ctttgtcttt | tccatcctca | 3960 |
| tcacaagccc | ttgtttgagt | gtcttatccc | tgagcaatct | ttcgatggat | ggagatgatc | 4020 |
| attaggtact | tttgtttcaa | cctttattcc | tgtaaatatt | tctgtgaaaa | ctaggagaac | 4080 |
| agagatgaga | tttgacaaaa | aaaaattgaa | ttaaaaataa | cacagtcttt | ttaaaactaa | 4140 |
| cataggaaaag | cctttcctat | tatttctctt | cttagcttct | ccattgtcta | aatcaggaaa | 4200 |
| acaggaaaaac | acagctttct | agcagctgca | aaatggttta | atgccccccta | catatttcca | 4260 |
| tcaccttgaa | caatagcttt | agcttgggaa | tctgagatat | gatcccagaa | aacatctgtc | 4320 |
| tctacttcgg | ctgcaaaacc | catgggttaa | atctatatgg | tttgtgcatt | ttctcaacta | 4380 |
| aaaatagaga | tgataatccg | aattctccat | atattcacta | atcaaagaca | ctattttcat | 4440 |
| actagattcc | tgagacaaat | actcactgaa | gggcttggtt | aaaaataaat | tgtgttttgg | 4500 |
| tctgttcttg | tagataatgc | ccttctattt | taggtagaag | ctctggaatc | cctttattgt | 4560 |
| gctgttgctc | ttatctgcaa | ggtggcaagc | agttcttttc | agcagatttt | gccactatt | 4620 |
| cctctgagct | gaagtctctt | gcatagattt | ggcttaagct | tgaattagat | ccctgcaaag | 4680 |
| gcttgctctg | tgatgtcaga | tgtaattgta | aatgtcagta | atcacttcat | gaacgctaaa | 4740 |
| tgagaatgta | agtattttta | aatgtgtgta | tttcaaattt | gtttgactaa | ttctggaatt | 4800 |
| acaagatttc | tatgcaggat | ttaccttcat | cctgtgcatg | tttcccaaac | tgtgaggagg | 4860 |
| gaaggctcag | agatcgagct | tctcctctga | gttctaacaa | aatggtgctt | tgagggtcag | 4920 |
| cctttaggaa | ggtgcagctt | tggtgtcctt | tgagctttct | gttatgtgcc | tatcctaata | 4980 |
| aactcttaaa | cacaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | aaa | | 5023 |

<210> 75
 <211> 1129
 <212> DNA
 <213> Homo sapiens

| | | | | | | |
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| gtttttatatt | tttttttttt | tgagatggaa | tttctctctt | attgcccgag | ctggagtgca | 120 |
| gtggcagcat | cttggctcac | ctcaacctcc | gcctcccggg | ttgaagcgat | tctccttctt | 180 |
| cggcctccc | agcagctggg | attacaggca | tgcgccacca | tgcccggcta | attttgtatt | 240 |
| tttagtagag | atgggggttt | tccatgttgg | tcaggctggt | cttgaactcc | ctacctcagg | 300 |
| tggtccacct | gcctgggcct | cccaaagtgc | tgggattaca | ggcgtcagcc | accgtgcctg | 360 |
| gcctgagaat | tcacattttt | aacaatttcc | caggggatgt | tagtgcagcc | tgtctgggga | 420 |
| ccatggttcg | agaaccatag | ctctagattt | ttctaagagc | atttctgtct | ccatgccaga | 480 |
| cctgttttcc | tccattgaagt | atactatttc | aatgctcgac | ttagtgttta | tgttttactc | 540 |
| tttctactgt | ttttacaatc | ttaattccagc | ctataaattc | ctctgggcag | aaattatacc | 600 |
| ttccacactc | tttcattttc | tgttttgtaa | aataatgagt | acatcttcag | catgattaat | 660 |
| aatagaatgg | agaaagggga | aaaacctcag | actatcaacc | ccagtaaaca | acatctccaa | 720 |
| gtggatatca | gccctagaat | tatcttacia | atttacattt | ctaacaagtt | cccagatgag | 780 |
| gccgatgctg | tagattcagg | gaccactctt | tgagaagaac | tttgacaggg | actttaagag | 840 |
| gatcaagtga | acagtctatt | atgtaagcca | ttaacacagt | ggctggcaca | aagtcagcct | 900 |
| tcaaaactgt | tagttgatgt | gacttttact | tgataaacgc | tcagataaat | cttgttaagt | 960 |

| | | | | | | |
|------------|------------|------------|------------|-------------|-------------|------|
| tgaacaaaat | gtttatcaag | ctcagctacg | gagtgattta | tttatgtgag | atggagtgac | 1020 |
| atttcatagg | aagcagtgct | taattacagc | tatgctcaca | cctgggtattg | ccagtggtgct | 1080 |
| actgaggtca | gttcccagcc | ccatgtgtaa | aaaaaaaaaa | aaaaaaaaaa | | 1129 |

<210> 76
 <211> 1889
 <212> DNA
 <213> Homo sapiens

| | | | | | | |
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| gggtggcgga | gaatgggaac | gcggcaccat | ggaggctctg | ctctctacgg | agattacccg | 120 |
| cacggaactg | ctgctgtgta | agctgatccc | ttattacttt | ctcgggatgc | tggcgatggt | 180 |
| gctgtgtatg | ctgggtgcag | tggtttattct | cggcgtgccg | tatcgcggtg | cgctgctgat | 240 |
| tctgtttttt | atctccagcc | tggttttact | cagtaccctg | gggatggggc | tgctgatttc | 300 |
| cacgattacc | cgcaaccagt | tcaatgccgc | tcaggctgcc | ctgaacgccg | cttttctgcc | 360 |
| gtcgattatg | ctttccggct | ttatttttca | gatcgacagt | atgcccgccg | tgatccgcgc | 420 |
| gggtgacgtac | attattcccg | ctcgttattt | cgctcagcacc | ctgcaaagcc | tgttcctcgc | 480 |
| cgggaaatatt | ccagtggtgc | tggtggtaaa | cgctgctgtt | ttgatcgctt | cggcggtgat | 540 |
| gtttatcggc | ctgacgtggc | tgaaaaccaa | acgtcggctg | gattagggag | aagagcatgt | 600 |
| ttcatcgctt | atggacgtta | atccgcaaag | agttgcagtc | gytgctgcgc | gaaccgcaaa | 660 |
| cccgcgcgat | tctgatttta | cccgtgctaa | ttcagggtgat | cctgttcccg | ttcgccgccca | 720 |
| cgctggaagt | gactaacgcc | accatcgcca | tctacgatga | agataacggc | gagcattcgg | 780 |
| tggagctgac | ccaacgtttt | gcccgcgcca | gcgcctttac | tcattgtgctg | ctgctgaaaa | 840 |
| gcccacagga | gatccgcccc | accatcgaca | cacaaaaggc | gttactactg | gtgcgtttcc | 900 |
| cggtgactt | ctcgcgcaaa | ctggatacct | tccagaccgc | gcctttgcag | ttgatccctg | 960 |
| acgggcgtaa | ctccaacagt | gcgcaaattg | ccgccaaacta | cctgcaacag | atcgtcaaaa | 1020 |
| attatcagca | ggagctgctg | gaaggaaaaac | cgaaacctaa | caacagcgag | ctgggtggtac | 1080 |
| gcaactggta | taaccggaat | ctcgactaca | aatggtttgt | gggtgccgtca | ctgatcgcca | 1140 |
| tgatcaccac | tatcggcgta | atgatcgta | cttcactttc | cgtcgcccg | gaacgtgaac | 1200 |
| aaggtagct | cgatcagcta | ctggtttcgc | cgctcaccac | ctggcagatc | ttcatcgga | 1260 |
| aagccgtacc | ggcggttaatt | gtcgccacct | tccaggccac | cattgtgctg | gcgattggta | 1320 |
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| tttatggttt | atcgctgggtg | ggattcgggtc | tggtgatttc | atcactctgt | tcaacacaac | 1440 |
| agcaggcggt | tatcggcgtg | tttgtcttta | tgatgcccgc | cattctcctt | tccggttacg | 1500 |
| tttctccggt | ggaaaacatg | ccggtatggc | tgcaaaacct | gacgtggatt | aaccttatcc | 1560 |
| gccactttac | ggacattacc | aagcagattt | atltgaagga | tgcgagtctg | gatatttgtg | 1620 |
| ggaatagttt | gtggccgcta | ctggtgataa | cggccacgac | agggtcagcg | gcgtacgcga | 1680 |
| tgtttagacg | taagggtgatg | taactttctta | tctttcgcca | gcaaagacac | taccgccggg | 1740 |
| ccggcaagga | ttgccagccc | tgcaattgcc | agcaaaaagt | tgttttccag | aacgcgggac | 1800 |
| aacagccaca | gcacaatcag | cgctgcgcca | aaataccagg | tcgtgggtcag | ctcttccagc | 1860 |
| acgtctgcca | cctcacgcca | gcgttgctc | | | | 1889 |

<210> 77
 <211> 845
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (807)
 <223> n equals a,t,g, or c

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| cacgaggagt | gctcgaggcc | ccacaatggg | cgctggattg | gatgtttggc | aactgattcc | 120 |
| gactggatgg | tgagctgggc | agactgtggg | atgggatggc | agctccgggc | cctgtcagct | 180 |
| gtgggcctgt | ggttcacagc | tggggactcc | cacctttctg | tccagggtctg | tggagggggc | 240 |
| ccagccctca | ccctctggca | cctccgatcc | tccacacca | ccaccatctt | ccccatccg | 300 |
| gcgcccacaga | agcactgcac | cttctaccag | gacctgggtga | ggccctgtgt | ctcacttctg | 360 |
| ccacccccac | tgactcttcc | cttcagtcct | gacccctgag | caccttccct | gtcctctgca | 420 |
| gattctgtca | gctggccagg | gccgctgcgt | caaccagtgg | cagctgagcg | gggagctgaa | 480 |
| ggcccagggtg | cctggctcct | ccccagggct | gctcagcctc | agcctcaacc | agcagcctgc | 540 |
| cgcgctgag | tgcaagggtg | gtccggcagg | ggccgcggag | cggttgggag | gcaggggtgt | 600 |
| gggcaggcca | gtcatgcccc | tctttcctcc | aggtcctgac | agctgcaggc | aacagctgcc | 660 |
| gggtggatgt | cttcaccaac | ctgggttacc | gagccttctc | cctgtccttc | tgatctctga | 720 |

| | | | | | | |
|------------|------------|------------|------------|------------|------------|-----|
| cgacaccccc | agccagctca | gggttttaga | gtgtttttca | ttttcttttt | tttttttttt | 780 |
| tacaataaag | tttcaggctt | ttttaaaaa | aaaaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | 840 |
| aaaaa | | | | | | 845 |

<210> 78
 <211> 1799
 <212> DNA
 <213> Homo sapiens

| | | | | | | |
|-------------|-------------|-------------|-------------|-------------|-------------|------|
| <400> 78 | | | | | | |
| gaattcggca | cgaggcagca | ttgaactcct | gggtcagat | gatctttcca | cctcagcctc | 60 |
| ccaagtagtt | gggacttttag | gcatgctctg | ccacgcctgg | ctattattga | tgtattttatt | 120 |
| tttagagatg | aggtctcact | gtgttgccca | gactggctctc | gaactcttgg | cctcaagcca | 180 |
| tcctcctttc | tcagcctcta | cagtagctgg | gatttcaggt | acatgccact | gtgccctgct | 240 |
| tattcccttt | aaaatacggg | aaccacaggg | aaggagggat | tcttccctgc | taatatttgt | 300 |
| ctgtccagtc | tctggcgctg | agcttggtgc | atgaaacccc | taacatttat | taggcattgt | 360 |
| ggaaagtact | tcccgtgtat | tgtctcagaa | acaacacagt | gtcccagaaa | aaacttgaga | 420 |
| gtcaagtggc | ccacagcggg | caagttgctt | attttctctt | aggtttctca | tctgtaaagt | 480 |
| gggaataata | ttagtacccc | cttgtaggat | gattataatg | tcttgtggct | acaagccaag | 540 |
| gaatgccagg | aattccttga | agccaataga | atgtcctatc | cctgctcgga | agctagaaga | 600 |
| ggcaagaaag | aattcttcat | taggaccttt | ggagagagca | tggccccggg | aacaccttga | 660 |
| tttcagactt | ctggcctcca | gaactgtgag | aggataaact | tccattgtct | tagacacca | 720 |
| gttcgtgggt | aatttgctac | agcagcccca | ggaaactaat | acaaggactg | aacatgtgaa | 780 |
| cactggtaaa | aaaaaaaaaa | aacaaaaaca | aaacctagaa | ctgtgcctgg | ccatagtaaa | 840 |
| tactatgtaa | atgtttgtga | aataaatcct | ttcttaaaaa | tgtcacagct | ccttgaggta | 900 |
| gggtgttattt | ttattcctat | attccagagg | aggaaactga | ggcttaggtc | aagcccataa | 960 |
| ctatgtgaca | aatgaaatat | cctccatgtt | ctctcatttc | ccccacttaa | ttggacctac | 1020 |
| cttttttaaa | gtcatttcag | ctgaggcttc | ttgaacattt | tatgacaccc | tttgcgtata | 1080 |
| gactgagagg | taacaggaaa | ttcatgtttt | gtttgggaaa | ggcctggcct | atgatgcggg | 1140 |
| aacaaatcca | cccagcacca | cgggtgtctgc | gtcatgcaga | gtctgggttac | tctccggggc | 1200 |
| agctgtgctc | tctgcagtcg | ttcctgatcg | aggctgcctc | attttgtgat | gccactatat | 1260 |
| caacctatgg | cttccaagat | atctgtgaca | aattaaaaaa | gagcatgatg | tgtatcatgt | 1320 |
| gtgctcatag | ctgtgggcct | gaatggatca | catggcatca | gattaactgg | aaaggttgtc | 1380 |
| ggtagctatg | gtcttccctt | gtgcccagga | agtggaaaaa | gaaataggat | ttgggggaaca | 1440 |
| tttagctttg | gctcgggtcac | agcctccaga | ctttaaagcc | acgtttttta | agccaaaggt | 1500 |
| agttgtgggg | cagggtgtgg | ggctcatgtg | cgtaatccca | gcactttggg | agactgaggc | 1560 |
| gggtggatca | cctgagggtca | agagctcaag | accagcctgc | ccaatgtggc | aaaaccccg | 1620 |
| ctctactaaa | aatacaaaaca | aaaaatttag | cggctgtggg | ggcgtatgct | tgtagtcca | 1680 |
| gctacttggg | aggctgaggc | aggagaattt | cttgaacccg | ggaggcgagt | gagccgagat | 1740 |
| ggcaccactg | cactccaacc | tgggtgacag | agcaagactc | tgtctcaaaa | aaaaaaaaaa | 1799 |

<210> 79
 <211> 2463
 <212> DNA
 <213> Homo sapiens

| | | | | | | |
|------------|------------|------------|-------------|------------|-------------|------|
| <400> 79 | | | | | | |
| tgcacccacg | cgtccgctcc | atctaggaca | agtcaggatc | gagatccaag | ttctctctcc | 60 |
| acctcagaaa | caacgggtgg | accttcattg | gggagtactg | aatttcagcc | acttgtgcag | 120 |
| tcaacaacac | ttctacctga | agcctcccat | gaccagtttg | tggctcaagg | tcaccaggaa | 180 |
| agtacatcac | cacggccacc | tcatgattca | tctctttctg | ctcccctgcc | caaactgtgt | 240 |
| gtttttgtta | ctccatctct | tctttcagca | atgtgcagcc | tcttggacaa | cctcttgacg | 300 |
| attgtctcca | gagacactgc | aaaggctttt | cgacaagctc | atctcataga | acttctctgt | 360 |
| agcattgcag | atgctaccct | catacagaca | tgtgtccagg | aactcagagc | cctgtgcctc | 420 |
| tcatcacctc | cagctgaaca | cactcagggt | caggtttctt | ttctcctgga | atacctatcc | 480 |
| tctttgtcca | ggcttctgca | gtcatgttta | ttgggtggagc | ctgaccttgt | gattcaggat | 540 |
| gagcttgtga | aacctcttat | caccaatatc | attggaattc | tcaccatatg | taccaaagat | 600 |
| gtattagata | aagagttaat | atcagctttt | tatcacacat | ggacacattt | atttaattct | 660 |
| ctggccatgc | tcttgaggaa | agctgggtgc | atcacactcc | cgtctgttac | cgtggccctg | 720 |
| gccaagcact | ggacagcggc | gattgatatg | ttctgcacat | gtgcaggctt | gtctgcccacg | 780 |
| tgtcctgccc | tgtatactgc | cagcttgcaa | ttcctttctg | ttctcttgac | cgaagaagca | 840 |
| aaagggcatc | tccaggctaa | gagcaaaaca | catttatgct | gtagtccaac | agtggcttca | 900 |
| cttcttgatg | actctcagga | aaatcagaaa | tctctagaac | aacttagtga | tgtaatcctt | 960 |
| cagtgtcatg | aagggaaatc | ctccaaagat | atcctgaaaa | gagtagctgc | aaatgcattg | 1020 |
| atgtcactgc | tggctgtcag | tagaagagca | cagaaacatg | ctttgaaagc | caatcttata | 1080 |
| gacaattgca | tggagcagat | gaaacacata | aatgcacaac | tgaacctaga | ttctctgagg | 1140 |

| | | | | | | |
|-------------|------------|-------------|-------------|------------|------------|------|
| cctgggaaag | cagcattgaa | aaaaaaggag | gatgggtgta | ttaaagagtt | aagcattgcc | 1200 |
| atgcagctcc | taagaaactg | tctttatcaa | aatgaggaat | gtaaagaagc | agctcttgaa | 1260 |
| gctcaccttg | tccctgtctt | gcactctctc | tggccttgga | ttttgatgga | tgattcattg | 1320 |
| atgcaaattt | ctctgcagct | cctttgtgtc | tatactgcaa | attttccaaa | tggttgcagt | 1380 |
| tctctttgtt | ggtcaagtgt | tggacaacac | cctgttcaag | ctacacatag | aggagccgtg | 1440 |
| agcaactctc | tgatgctgtg | tatcctaaag | ttggcttccc | agatgccact | ggagaacacc | 1500 |
| acggttcagc | agatggtttt | tatgcttctt | tcaaacctgg | ccttgctgca | tgactgtaaa | 1560 |
| ggagtaattc | agaagagtaa | cttcttacag | aacttctctt | ctctagcatt | gccaaaagga | 1620 |
| ggaaataaac | atctaagtaa | tctgactatt | ccttggttga | agttactcct | gaatatatca | 1680 |
| tctggagaag | atgggcaaca | aatgattctg | aggcttgatg | gctgtctaga | cttactaaca | 1740 |
| gagatgagca | aatacaagca | caagagcagc | cctttattgc | ctcttcttat | ctttcataat | 1800 |
| gtttgcttca | gtcctgcaaa | taaaccceaag | atcctggcta | atgaaaaagt | cattactgtg | 1860 |
| ccttgctgcct | gtctggaaag | tgagaatcaa | aatgctcaga | ggattggagc | agctgccctt | 1920 |
| tgggctctga | tttacaatta | tcagaaggca | aaaacagctt | tgaaaagccc | atcagtaaaa | 1980 |
| agaagagtgg | atgaagcata | ctccttagca | aagaaaactt | tcccaaactc | agaagcaaac | 2040 |
| cctctaaatg | cctattatgt | gaaatgtctt | gaaaacctcg | tgcagctcct | tattcttctt | 2100 |
| gagtgccatg | ggatgctaca | ccttgaagct | gacagtcac | aacaggggag | ctaaagttag | 2160 |
| agccagctgt | gtgtagcagc | tgttacctga | agacgtgcta | cctctctaca | aagtgttgat | 2220 |
| ccccttcttt | cccatgagag | agagaactgg | tgatactcca | acaccgtcca | gttgtggcag | 2280 |
| ctctccagaa | gtaatagcag | ctgacaactt | tctgtgcctt | ttcctttctg | ttgaaaaggc | 2340 |
| atagaaagt | ctgggaacat | aaacattttt | acccttttct | atgccattta | ttttgtaaaa | 2400 |
| atcctattta | acagttatgt | aataaaacaa | tattttttaga | aactaaaaaa | aaaaaaaaag | 2460 |
| ggc | | | | | | 2463 |

<210> 80

<211> 1168

<212> DNA

<213> Homo sapiens

<400> 80

| | | | | | | |
|-------------|-------------|------------|-------------|-------------|------------|------|
| ccacgcgtcc | gggcctctgt | tgatgctcct | cagcctactc | gggaacgtga | aggggcagct | 60 |
| ggcgaaaggg | catttctggg | gccacttgct | ctgccccact | gataaggcac | acccgcggtg | 120 |
| cactgtgagc | tctttgagga | ctgaggccag | gggatgcctc | ctggaacctg | ccaggcctct | 180 |
| ctgtttctgtg | aagggtcagta | tccacttgat | tcctccaggc | ggcgtctccag | gtgggaggag | 240 |
| cagggctcttc | tgctgtttcc | aaaggaatgg | ccatgacact | gcttttgacc | ttagaagtgg | 300 |
| attcagggac | ccagcaaaag | gcgggggtgg | gttcccaggg | acaggcagtc | ctcccggggc | 360 |
| ttacatgctt | tttgctaact | ttcctattag | cagcttcagt | ttatatcacc | cagagtgcgt | 420 |
| gggataatgt | tgaagtcgct | gaagttacgg | gttattttat | gtttttacat | gggatttttc | 480 |
| tgtttttgat | tggaagaagg | agacagaaat | tggaaggaaat | gggattatta | tcctagggaa | 540 |
| gggcccgttg | caaggagtgt | agccggcccc | tctgagccct | gggggctatc | tgacctgaag | 600 |
| cctggacact | gggccccttca | ggtcgcaaga | aaaagttccc | tcctaaattc | tattaggatt | 660 |
| ttggagaatt | tttgacagt | aagaagctct | ttgggcttct | caaaagggaa | 720 | |
| aagttcaatt | caaagattgt | aaactacgaa | gtattccagc | cgtgttgctg | atctagttgg | 780 |
| atagttgtac | ctcaaaaaag | taggtgagaa | ctggcttctt | cattgtccca | ggatgtcaaa | 840 |
| tactaatgac | ataagagctc | acttacgtgc | caaaattcac | ttttatacta | gtttttcagt | 900 |
| gctttaatat | ttgtaactta | aattttaaaa | ctcgtattta | caaacactac | tgtaacttca | 960 |
| gtgaaactga | attgtgcgat | tgaagctttt | tgcttatcat | agtattttat | acactactta | 1020 |
| attcagtaaa | tatataaaa | tagccttcaa | tttattttta | tattatttta | catgttttta | 1080 |
| cctgcagttg | tgtatgtgaa | tttaccttgg | taatcgagat | gtcatgctaa | ggaccaataa | 1140 |
| actatcactg | aacaaaaaaa | aaaaaaaa | | | | 1168 |

<210> 81

<211> 1707

<212> DNA

<213> Homo sapiens

<400> 81

| | | | | | | |
|-------------|------------|-------------|-------------|------------|-------------|-----|
| tcgaccacag | cgtccgattt | aaatcaccat | catctcttat | ctggattctt | tcagttacct | 60 |
| cctgattaat | tccctgcttc | ttgtgttgct | ttccacagat | cactgcctgc | atagcaaaaca | 120 |
| gaatgatttc | ctaaaaaaaa | aaaatttgaga | ctgtattgtt | cccttgctta | aagccctcca | 180 |
| acagcttccc | attgcaataa | aaataaatgt | caccttctta | tttggcctat | aaggcctgac | 240 |
| gtggtttggc | tcctgcctct | gtaaactcat | catctacccc | ttgtccccag | gttctcatgc | 300 |
| tccagccaca | gtggctacct | tcctgtcccc | cgaatgtacc | cagtatatac | tacctcagac | 360 |
| ttttgtctctg | gaacattcgt | tctcattttt | gcattggctaa | ccctttctga | attagtcagg | 420 |
| gtttctccata | gaaagataat | caattgggtt | tttatatttt | taaggagatt | ttattatgga | 480 |
| gaattagcat | atgcaaatat | ggagaccaca | atgtgccatc | tacaagctgg | agaccacaaga | 540 |

| | | | | | | |
|-------------|------------|-------------|------------|-------------|-------------|------|
| cagctggtgg | tgtaattcag | tctgagtcgg | aaggctgaga | gccagaggaa | ctgatggtgt | 600 |
| gaatcccagt | ctgaaggcaa | gggaagatga | aatgagattt | cccagctcaa | gtggtgagac | 660 |
| aagaaacaga | gaagggggga | caaattcctc | tttcttccat | gttttgttct | attcaaaatg | 720 |
| gattggctga | tgcccacagt | ggggaggggca | atatgtttta | ccgagtgccac | tgattccaat | 780 |
| gctaattctca | tccggaacc | ctcacaaa | caccagaaa | cgatgtttta | tctggacatc | 840 |
| ccatgcaagg | tcccgtaag | ttgacacaaa | aattaacat | cacactttcc | cgcagtgttg | 900 |
| gtttcagctc | aaacattttt | ccctcagata | ggccttctct | gaccatcttt | ctaacttcat | 960 |
| gtccaagaca | tcctttgttt | cgctatctaa | ttatatgtga | ttcagggctt | gacatgtgct | 1020 |
| tccaccctgc | tcctctaaat | agacaaaaat | tttggccatg | tgctgaattg | accacggtgt | 1080 |
| ggaggaagac | atattctcct | gcattcatcag | tggggaatgc | atgcattggc | taaaaacctc | 1140 |
| tttagagggc | actgttacag | tatccattag | aactaaaact | atagcttcat | gagggaaga | 1200 |
| gactatggcg | atagtaggag | ttcagtaact | tgttgaaaga | atggtgaatt | tgaagattaa | 1260 |
| atcacagagt | atctgattcc | agttcttttt | aacttctctt | ttttctccat | agctttcatc | 1320 |
| ccatatttaa | aatgtcctct | gctaagatgc | caacacatat | cctttaaagt | aaaaattccta | 1380 |
| gctgggagca | gtggctcacg | cctgtaatcc | cagcattttg | ggaggctgag | gcgggcggat | 1440 |
| cacttgaggt | taggagttca | agaccagctt | gaccaatatg | gtgaaacctt | gtctctacta | 1500 |
| aaaatacaaa | aattagctgg | gtgtgggtgg | acgtgcctgt | agtcccagtt | actcaggagg | 1560 |
| ctgaggcagg | agaattgctt | gaaccggga | ggtggaggtt | gcagtgaacc | gaggtcacac | 1620 |
| cattgcactc | cagcctgggc | aacagaatga | gactctgtct | caaaaaaag | aaaaaaaaa | 1680 |
| aaaaaaaaa | aaaaaaaaa | aaaaaaa | | | | 1707 |

<210> 82

<211> 1480

<212> DNA

<213> Homo sapiens

<400> 82

| | | | | | | |
|-------------|------------|-------------|------------|------------|-------------|------|
| ggcacgagcg | gcacgagtga | acatccatgt | actcaccatc | tctttacctt | cttccctccc | 60 |
| tccctccctt | cctccagttg | agtctctcca | gaagcccccg | attcaacaag | gggttacaaa | 120 |
| gagccatgga | gaagacaatg | aagggttcta | caattaagat | tttgctctat | tttttccatc | 180 |
| atatctatgc | atctctccat | acctttattc | ctctacccaa | tccatctatt | tttttatgca | 240 |
| tttcaaagta | cattgcagac | attagtacat | gacacctcta | atcagtttta | tgttcctttc | 300 |
| ctttttactt | tatacgaaat | aaaaatcaca | gttaacaatt | atcaagtgtc | tactgtcagg | 360 |
| cactgtgcca | agcactttcc | ttgcattaca | taatttgaat | ctcatggtaa | ccctataagt | 420 |
| acagttacca | ccttcatttt | acaaatgaga | agaactgaaa | cagagaacaa | tgggtgcaat | 480 |
| taacattttta | aaagtctttc | tatgggccat | tcacagtgc | agtacttttc | atgcattatc | 540 |
| tcagttaatc | ccttatagca | atttcataaa | ggcaatacta | ttacagatga | caaaattgag | 600 |
| actttgagaa | aaagatcctg | caaccttaata | agcatcagaa | cctgggtttg | aattgaggga | 660 |
| gtctgactcc | actatgcttg | gcttcgccat | tggttagcca | ccctattgta | gcatttgtct | 720 |
| ttgctattgt | gttttagctt | tttgggtcca | cttatgtttc | tcaccagact | gtggtctctc | 780 |
| aagttcagat | catgttttag | tcttcttagt | tccaggccat | cattcagata | caagtaggca | 840 |
| cttcatagat | gtttcctgaa | tggattcaca | aacaatgaat | agtaatagct | gaaagcctta | 900 |
| catcttagaa | cgaagtaaaa | cagtgacat | tctagaaaat | gcaatgaaaa | tcttgaaaac | 960 |
| tgatgatagg | tcctgttgat | aatttctctga | ggttttcttt | acaccaacag | gatttctctga | 1020 |
| gtaacctgga | gatgcgagag | acagcctggg | ggagttcagt | gctcttgcca | gcccaggcag | 1080 |
| gagcacacgc | ccataccctt | tggctcacca | ggcatctttt | ataagcccac | tgtgtggcaa | 1140 |
| acaccaggct | aagggatggg | gaggacacag | aggctaaacc | tgcaaggccc | catcttacgg | 1200 |
| agcacatagg | ctaacagggc | ataggaagag | actagcacat | tcataaccat | gacaaaagtc | 1260 |
| atgatgggca | cttcacaaga | aagagacaaa | ccagtttttt | aaagcaattc | caaggaagga | 1320 |
| gaaattagat | tatggtgtag | agaagaggct | cagcgacacc | ctgttgggga | aattttattt | 1380 |
| gggatgggca | caattttcaa | taatagaaat | gtggcaggga | gtaaatgagc | aaagatggga | 1440 |
| aatgcagtc | ccatgatgcc | tcgtgccgaa | ttcggcacga | | | 1480 |

<210> 83

<211> 425

<212> DNA

<213> Homo sapiens

<400> 83

| | | | | | | |
|-------------|-------------|-------------|------------|------------|------------|-----|
| tcgacccacg | cgctccgctag | ttctagatcg | cgagcgccgc | cctttttttt | tttttttttt | 60 |
| tttttttttt | ttttttttac | atcttttgga | aagggtaaaa | aagcatatat | gaaattaaaa | 120 |
| atagtatcaa | agaattcaac | tacaaagggc | ttacaaaact | tcgtaaatg | gagatatata | 180 |
| ggacattgta | cctaacctaa | tagaaaactta | aacatttttt | agttatgtat | gtcagttttt | 240 |
| aacctgttgc | catagaggaa | tgtaacaat | gtctaaaaaa | tcagtgtcat | acaaaatcag | 300 |
| ttatttccagc | caggcatggc | agctcatgcc | ggtaatecta | gtgctttggg | aggctgaggc | 360 |
| aggaggatca | cttgaagcca | ggcaagacca | tatagtgaga | ctctgtctct | gcaaaaaaaa | 420 |

aaaaa

425

<210> 84

<211> 1732

<212> DNA

<213> Homo sapiens

<400> 84

| | | | | | | |
|-------------|-------------|-------------|-------------|-------------|------------|------|
| ggcacgagac | atccattgaa | gctgcaacac | cacccccgcg | cacttcacct | ccttcctgac | 60 |
| atgctctgct | cctcctttct | ccccctcagc | actgctgcc | tctgggctgc | attattctcg | 120 |
| ggtatggggg | ctgtccgaca | ttccccatca | gaaggaaaaa | gatccctgaa | aagtagcagg | 180 |
| tgcttacatt | tctggcctct | accacccggc | tgcagtagtc | ccccaccacc | ctgcaatgtg | 240 |
| acaacaaaaa | atgtctctag | atgttgccag | aagtcctcta | gagatgggag | ggtacgactg | 300 |
| ccaccccgct | gagaattcct | gctgtcactg | gagtgggggc | tgttttctct | cccatgcctc | 360 |
| tggtaccttg | gggggtcccc | ctgctcccaa | gggctgcttc | caccaccctg | tccatccatc | 420 |
| ccgattggct | cccaggagggt | tttagctccg | ggcttcctgt | ctccacacac | actcctcaca | 480 |
| gttctccatg | atttcaacat | ccagggtggg | gacgcagcct | ctcggttctt | tgacctctcg | 540 |
| gggtgatcctg | ctgcttctac | cgggcccaacc | agtactccta | ggagccctca | caatttgacc | 600 |
| ctcaggcatc | ccattgtctg | cctgggtgcca | cctttctttg | gctctgtccc | caacggggtc | 660 |
| ttcactccat | taatgccatc | agcctctgac | ccagctccaa | accagctgtc | tagtaacccc | 720 |
| cgtcgcgcat | cctcaacatc | cgggtccccc | tcttgcatg | ctgcaatcat | ttggtgaaag | 780 |
| cacaacccaa | atgaaactca | agcttggtctg | ggcacgggac | tcacacctat | aatcccagca | 840 |
| ctttggggagg | ccaaggcagg | tgaatcgctt | tgagctcagg | agttcaagag | cagcaagacc | 900 |
| ccatctctac | aacaacaaaa | caaaaatcag | ccagggtggga | tggcgcaaac | ctaaaatccc | 960 |
| agctactcag | gaggctgagg | tgggacgata | agtggagccc | cagagggtcaa | ggctgcagtg | 1020 |
| agccatgatc | tagccaatgc | acttaccctg | gatggacaga | gtgagaccct | gtctcaaaaa | 1080 |
| acccaaaacc | cactctccac | cttttccccc | agagcaggcc | ttgctcaggg | gtcctccccc | 1140 |
| acccctccct | catcttctca | ctctctgctg | cttttcaact | tttctttgaa | cttatgatcg | 1200 |
| ctcctcccca | ttctctctca | gctgggggac | ttacttctca | cttaactcaa | aagcagaagt | 1260 |
| gatcatgaaa | cgtgcacaag | ctcccactgc | ctcatcatcc | tacctccgtg | cacctctgta | 1320 |
| cacttctatt | ttttttccat | ttctatgctg | aaccctctgg | caccaaccga | ggccaacacc | 1380 |
| tccattggac | ccgaccctct | tgttcactca | agcacattgc | tccaaaaatc | cttatttttg | 1440 |
| aagggttttct | ctttcatttg | ctccatcagc | aaatgggaata | acctcttagc | cccatgtcta | 1500 |
| ccttgctacc | cttactacaa | aactggacgt | gaatgccgaa | accctgtctc | tacaaaaaaa | 1560 |
| tataaaaaatt | agccagggtgt | ggtgggtgcat | gcctatagtc | ccagctactc | aggaggctga | 1620 |
| ggcacaagaa | tggcttaaaa | ccgggagaga | gagggtgcag | tccagcctgg | gtgacagagt | 1680 |
| gagactcggt | ctcaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | aa | 1732 |

<210> 85

<211> 2131

<212> DNA

<213> Homo sapiens

<400> 85

| | | | | | | |
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| ccacgcgtcc | gcccacgcgt | ccgcggacgc | gtgggcgcgc | tttcggctgc | gagctctctg | 60 |
| tggtgctggc | agcgacatgt | ggcgccctcc | gggactcctg | ggccgagctc | ttccccgtac | 120 |
| actgggacct | agcctctgga | gggtgactcc | taagtcacac | agcccagatg | ggcctcagac | 180 |
| tacctctctc | actttgtctg | ttcctgtgcc | taacctcgac | aggtcaggtc | cccatggccc | 240 |
| aggcacgagc | gggggtccaa | ggtcccatgg | atggaaggat | gccttccaat | ggatgtcttc | 300 |
| ccgtgtctcc | ccgaacaccc | tatgggatgc | catatcttgg | ggcactctgg | ccgtgctggc | 360 |
| cctgcagctg | gcaaggcaga | tccacttcca | ggcatccctg | ccagcaggac | ctcagcgggt | 420 |
| agaacactgc | tcctggcaca | gtccctctga | ccgtttcttc | tcactctcct | tgtggcaccc | 480 |
| atgctcctca | ctgcgacaac | acatcctccc | cagcccccgt | ggcccagctc | ccaggcacac | 540 |
| tggcctcagg | gaaccagggc | ttggccagga | agaacctca | gctcagcccc | ggaactcttc | 600 |
| acacaactct | ttgagaggag | ctcgtcctca | ggaccctctt | gagggaaggc | ccggtgattt | 660 |
| tggcttctctg | catgccagta | gtagcatcga | gtccgaggca | aaaccagccc | agcctcagcc | 720 |
| cactggtgaa | aaggaacaag | ataaatcaaa | aactctttcc | cttgaggagg | ctgtgacttc | 780 |
| cattcagcag | ctcttccagc | tcagtgtttc | catcgctttc | aacttccctg | gaacagagaa | 840 |
| catgaagagt | ggcgaccaca | cggcagcctt | ttcttacttc | cagaaagctg | cagccccggg | 900 |
| ctacagcaaa | gcgcagtaaa | atgcgggctt | gtgtctatg | catggcagag | gcacccccag | 960 |
| ggacattagc | aaggcgggtcc | tttattatca | gttggctgcc | agccaggggc | acagcctggc | 1020 |
| tcagtaccgc | tatgccagggt | gcctactacg | agacccagcc | tcttcgtgga | accctgagcg | 1080 |
| gcagagggca | gtgtccttgc | tgaagcaggc | tgcagactca | ggcttgagag | aggcccaagc | 1140 |
| tttctctggg | gtgcttttca | ccaaggagcc | ctacctggat | gagcagagag | ctgtgaaata | 1200 |
| tctttggctt | gcagccaaca | atggggatag | cgatctcagt | ggacaagcat | gttggggatg | 1260 |
| aagcctgata | agagaaggga | ttttggaact | ggtactgagt | tcttctgtgc | ttaggagatt | 1320 |

| | | | | | | |
|-------------|-------------|------------|------------|-------------|-------------|------|
| gttgatagg | agccttggcc | tggcttcaag | ccttagtcgc | tcactgactt | actgtgtgac | 1380 |
| cgttgggcag | ttgcagtagt | acgccagagc | tggcttgcac | caggctgtga | gagctgttgg | 1440 |
| cagcttaaaa | tctgctatgg | tgggaatatt | tgcaccacag | aaattgctaa | atgccataaa | 1500 |
| acagggcttt | ttccctcctc | gagagccagt | tggtcaacat | ttaccagcac | actactgggc | 1560 |
| ctggctcactt | cctgattcaa | acctgtttcc | tcgtctttaa | aatcagaata | ataatgcttg | 1620 |
| ccttacctgt | ccagtacttc | acaggggtgt | tgtgaggatc | aaaatctaac | tgagataact | 1680 |
| aacaggtgtg | acagtgtctg | gaaacctgta | cacatgaaaa | acacatcatt | acaagtgtatg | 1740 |
| gtaaccagag | gaaattagaa | gacgcacata | gtggagacag | taaacaggga | acactgtctca | 1800 |
| gtttgggggtg | ggtgggggatg | tctgggtgtc | tgtgaactgg | ggtcattggc | attcagacaa | 1860 |
| ttcagatgtg | ttccatgaag | cattagttct | ctgggatgct | tgtaatgtcat | aagaggaaaa | 1920 |
| aaatgggttag | atggggttgg | gaaatactga | gttaaacagt | taatatagga | agtctcaaag | 1980 |
| ctttatgtca | ctgtagatca | ctgaaaaggc | catctgtaat | ttgctgtatt | cctcaagtgt | 2040 |
| atgtgaccag | tatatctttt | gagttgcata | ttgaaggacc | aggagtcttg | gattaaatca | 2100 |
| agcaatatat | gcgtgaaaaa | aaaaaaaaaa | g | | | 2131 |

<210> 86
 <211> 1143
 <212> DNA
 <213> Homo sapiens

| | | | | | | |
|-------------|-------------|------------|-------------|-------------|-------------|------|
| <400> 86 | | | | | | |
| cgcgctccgag | cagatctgag | gacatctctg | tgccaggcca | gaaaccgccc | acctgcagtt | 60 |
| ccttctccgg | gatggacgtg | gggcccagct | ccctgcccc | ccttgggctg | aagctgctgc | 120 |
| tgtctctgct | gctgctgccc | ctcagggggc | aagccaacac | aggctgctac | gggatcccag | 180 |
| ggatgcccgg | cctgcccggg | gcaccaggga | aggatgggta | cgacggactg | ccggggccca | 240 |
| agggggagcc | aggaatccca | gccattcccg | ggatccgagg | acccaaaggg | cagaaggagg | 300 |
| aaccgcgctt | accgcggccat | cctgggaaaa | atggccccat | gggagagcca | ggtgaggagg | 360 |
| gcagatacaa | gcagaaattc | cagtcagtg | tcacggtcac | tcggcagacc | caccagcccc | 420 |
| ctgcacccaa | cagcctgatc | agattcaacg | cggctctcac | caaccgcag | ggagattatg | 480 |
| acacgacac | tggcaagttc | acctgcaaag | tccccggcct | ctactacttt | gtctaccacg | 540 |
| cgctgcatac | agccaacctg | tgcgtgctgc | tgtaccgcag | cggcgtcaaa | gtgggtcacct | 600 |
| tctgtggcca | cacgtccaaa | accaatcagg | tcaactcggg | cgggtgtgctg | ctgaggttgc | 660 |
| aggtggggcga | ggaggtgtgg | ctggctgtca | atgactacta | cgacatggtg | ggcatccagg | 720 |
| gctctgacag | cgtcttctcc | ggcttccctg | tcttccccga | ctagggcggg | cagatgcgct | 780 |
| cgagccccac | gggccttcca | cctccctcag | cttctctgcat | ggaccacact | tactggccag | 840 |
| tctgcattct | tgcctagacc | attctcccca | ccagatggac | ttctcctcca | gggagcccac | 900 |
| cctgacccac | ccccactgca | ccccctcccc | atgggttctc | tccttctctt | gaacttcttt | 960 |
| aggagtcaact | gcttgtgtgg | ttcctgggac | acttaaccaa | tgccttcttg | tactgccatt | 1020 |
| cttttttttt | tttttttcaa | gtattggaag | gggtggggag | atatataaat | aaatcatgaa | 1080 |
| atcaatacaa | aaaaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | 1140 |
| aaa | | | | | | 1143 |

<210> 87
 <211> 641
 <212> DNA
 <213> Homo sapiens

| | | | | | | |
|------------|------------|-------------|------------|-------------|-------------|-----|
| <400> 87 | | | | | | |
| tcgacccacg | cgtccgccat | ccggccccgag | attagggagg | attgactgtg | tcagggatgg | 60 |
| cggttgccct | ctctcgctgc | cagggccctt | gtcagagcag | ccaggctgga | cagacggcct | 120 |
| ccctcctctc | catctgaccg | gcacctgctg | cttcggggct | taggccaccg | ctccctgtcc | 180 |
| ccagaggaga | tagccccaga | tggactggaa | tggttgggca | tgagagcgca | tgtgtgcatg | 240 |
| ggccccgctg | tgggtccctc | tctgtccctc | catctgtatg | tgttctgtgt | cccttgcattg | 300 |
| tgtgctgtgt | agagtgcagc | cgtatgcata | aactcattgg | gctcttggct | gctcacaagg | 360 |
| caaatttgac | ttggaaagac | tttcatctcc | ttggaaccaa | gacttctctga | gtccccctca | 420 |
| ccctggccct | gttccaccat | ggttatctgg | gtattgggga | atggaaactt | tgggggagtg | 480 |
| acttttttaa | gagacactta | taatttctac | tactgcacta | ctgtccattg | tgggatgatt | 540 |
| aaacatggta | tttaactgtg | aaaaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | 600 |
| aaaaaaaaaa | aaaaaaagga | cgaacagacc | aaaaaaaaag | g | | 641 |

<210> 88
 <211> 1524
 <212> DNA
 <213> Homo sapiens

<400> 88

| | | | | | | |
|------------|------------|-------------|------------|-------------|------------|------|
| gaattccccg | gggaagaaca | gcgctccccg | ggccgcggga | gcctgcagag | aggacagccg | 60 |
| gcctgcgcg | ggacatgcg | ccccaggagc | tccccaggct | cgctgtcccc | ttgctgctgt | 120 |
| tgctgttgct | gctgctgccg | ccgccgccgt | gccctgcccc | cagcgccacg | cgcttcgacc | 180 |
| ccacctggga | gtccctggac | gcccgcgcagc | tgcccgcgtg | gtttgaccag | gccaagttcg | 240 |
| gcattctcat | ccactgggga | gtgttttccg | tgcccagctt | cggtagcgag | tggttctggc | 300 |
| tttaccttgt | gggggtcaga | atattcgtgg | aactggaatg | ccatagatga | ggggcccaag | 360 |
| agggacattg | tcaaggaact | tgaggtagcc | attaggaaca | gaactgacct | gcgttttgga | 420 |
| ctgtactatt | ccctttttga | atggtttcat | ccgctcttcc | ttgaggatga | atccagttca | 480 |
| ttccataagc | ggcaatttcc | agtttctaag | acattgccag | agctctatga | gttagtgaac | 540 |
| aactatcagc | ctgaggttct | gtggtcggat | ggtgacggag | gagaaccgga | tcaatactgg | 600 |
| aacagcacag | gcttcttggc | ctggttatat | aatgaaagcc | cagttcgggg | cacagtagtc | 660 |
| accaatgac | gttggggagc | tggtagcatc | tgtaagcatg | gtggcttcta | tacctgcagt | 720 |
| gatcgttata | accaggaca | tcttttgcca | cataaatggg | aaaactgcat | gacaatagac | 780 |
| aaactgtcct | ggggctatag | gaggggaagc | ggaatctctg | actatcttac | aattgaagaa | 840 |
| ttggtgaagc | aacttgtaga | gacagtttca | tgtggaggaa | atcttttgat | gaatattggg | 900 |
| cccacactag | atggcaccat | ttctgtagtt | tttgaggagc | gactgaggca | aatgggggtc | 960 |
| tggctaataa | tcaatggaga | agctatttat | gaaacccata | cctggcgatc | ccagatgac | 1020 |
| actgtcaccc | cagatgtgtg | gtacacatcc | aagcctaaag | aaaaattagt | ctatgccatt | 1080 |
| tttcttaaat | ggcccacatc | aggacagctg | ttccttggcc | atcccaaagc | tattctgggg | 1140 |
| gcaacagagg | tgaactact | gggccatgga | cagccactta | actggatttc | tttgaggcaa | 1200 |
| aatggcatta | tggtagaact | gccacagcta | accattcatc | agatgccgtg | taaattgggg | 1260 |
| tgggctctag | ccctgactaa | tgtgatctaa | agtgcagcag | agtggctgat | gctgcaagtt | 1320 |
| atgtctaagg | tcaggaacta | tcaggtgtct | ataattgtag | cacatggaga | aagcaaattg | 1380 |
| aaaactggat | aagaaaatta | ttttggcagt | tcagcccttt | ccctttttcc | cactaaattt | 1440 |
| tttcttaaat | tacctatgta | accattttta | ctctccagtg | cacttttgcca | ttaaagtctc | 1500 |
| ttcacattaa | aaaaaaaaaa | aaaa | | | | 1524 |

<210> 89

<211> 1810

<212> DNA

<213> Homo sapiens

<400> 89

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| ccacgcgtcc | gtacatgctg | gccagctgaa | aaatggagac | tttcattttca | ctgactgttt | 60 |
| attttttggg | tcactgatgt | ctgctacaga | tccagtgaca | gtgctggcca | ttttccatga | 120 |
| actgcacgtg | gaccttgacc | tgtacacact | cttgtttgga | gagagtgtgt | tgaatgatgc | 180 |
| agtggccata | gtccttacat | attctatata | catttacagt | cccaaggaga | atccaaatgc | 240 |
| atltgatgcc | gcagcattct | tccagtctgt | ggggaatttc | ctgggaatct | tcgctggctc | 300 |
| atltgcaatg | gggtctgcgt | atgccatcat | cacagcactg | ttgaccaa | ttaccaagct | 360 |
| gtgtgagttc | ccgatgctgg | aaaccggcct | gtttttcctg | ctttcttgga | gtgccttctc | 420 |
| gtctgccgag | gctgccggcc | taacagggat | agttgtctgt | ctcttctgtg | gagtcacaca | 480 |
| agcacattat | acctacaaca | atctgtcttc | ggattccaaa | ataagaacta | aacagtgtgt | 540 |
| tgaatttatg | aacttttttg | cggagaacgt | catcttctgt | tacatggggc | tggtactgtt | 600 |
| cacgttccag | aatcatatct | ttaatgctct | ttttatactt | ggagcctttc | tagcaatttt | 660 |
| tgttgccaga | gcctgcaaca | tatatccctc | ctccttcctc | ctgaatctag | gccgaaaaca | 720 |
| gaagatcccc | tggaactttc | agcacatgat | gatgttttca | ggtttgcgag | gagcgatcgc | 780 |
| atltgcttca | gctatttcgga | acacagaatc | tcagcccaaa | caaagtatgt | ttaccactac | 840 |
| gctgtccttc | gtgttcttca | ctgtctgggt | atltggagga | ggaacaacc | ccatgttgac | 900 |
| ttggcttcag | atcagagttg | gcgtggacct | ggatgaaaat | ctgaaggagg | acccctcctc | 960 |
| acaacaccag | gaagcaaata | acttgataa | aaacatgacg | aaagcagaga | gtgctcggct | 1020 |
| cttcagaatg | tggtatagct | ttgaccacaa | gtatctgaaa | ccaattttta | cccactctgg | 1080 |
| tcctccgctg | actacaacat | tacctgaatg | gtgtgggtccg | atltccaggc | tgcttaccag | 1140 |
| tcctcaagcc | tatggggaac | agctaaaaga | ggatgatgtg | gaatgcattg | taaaccagga | 1200 |
| tgaactagcc | ataaattacc | aggagcaagc | ctctccacc | tgagtcctc | ctgcaaggct | 1260 |
| aggtctggac | cagaaagctt | caccccagac | gccaggcaag | gaaaacattt | atgagggaga | 1320 |
| cctcggcctg | ggaggctatg | aactcaagct | tgagcaaact | ttgggtcaat | cccagttgaa | 1380 |
| ttaattggca | tgaagagtac | agatgtaatc | acaagtaatg | caagactcac | tgaggaatac | 1440 |
| aagccaagct | gatgaggcag | tacaggggag | aggctggaaa | acatattaag | agcataaatt | 1500 |
| ggagagaatc | aaagccttgt | cacatggatc | ctgggtgcctg | aagaaatgag | atltttattat | 1560 |
| ccctctctat | tatgcaaatg | aatttagttt | tttgacagca | gccattctga | ttactgtgatt | 1620 |
| ggctgggggtg | gggatggagg | tatcaggagt | ctagctgctg | gaggatggga | cagctgtgct | 1680 |
| gggtcttcag | ggcatttctg | ctgcgaatgc | ggctctccag | gcccttcact | tctattcttg | 1740 |
| atlttatcc | ctccattaa | gagagtttaa | aaataaaaga | aagcttctga | gagtaaaaaa | 1800 |
| aaaaaaaaaa | | | | | | 1810 |

<210> 90

<211> 1617
 <212> DNA
 <213> Homo sapiens

<400> 90
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 atttcatgcc ccttaagaca gtttcataat tatgaaaata gttgttaggg attttccaag 120
 ggaacaacat cagtatttac acaaggaagg cctttgtatt tttaaaattt ctactgtagc 180
 tataattggg tcccattggt attttctaata ctataaattt gtgcattctt tttctttatc 240
 cactttttatg gaagatgggtg tgttttaata actttttttt aacttagctt ttgattttgg 300
 atatttttgtc cattgattac cagtgatttt ttcttttctt acaggagctt ttaagtcac 360
 agttttccctg tgcatagtgc ttttagctgac tcctaaaagt tttgctatgc agtggttggt 420
 aatcactccc aggccttttct actttccatt attacttctg tggcttggtga gtgttaaatt 480
 tcttttttatt ttcatttttg gtgatgggca gggctctgct ccatcactca ggccggagtg 540
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 caagtgatcc acctacctca gactcccaaa gtgcttggat tacaggcgtg agccaccaca 780
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 tttgctatgc atagttaatt ttgtaaatat tccacatacg cttgaaaaca atatatgttt 960
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 ggaaaggtag attagacaag gcacctggta ctctttttgc ctgttgcaaa attgttcaca 1140
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 gcagcctccg ctctgtgggt tcaagcgatt ctctgcctc agcctcctga gtagctggga 1320
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 tatcaccaca tacaagaatt gtgcactttc atgaactatt ggaacaggtc tgtaagtagc 1560
 aaaaaaccaa aaaaaaagg aattcgatat caagcttatc gataccgtcg acctcga 1617

<210> 91
 <211> 758
 <212> DNA
 <213> Homo sapiens

<400> 91
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 cacacacaca cacacacaca cacacacaaa acttcacagc aggccagctg cagtgacttg 420
 tcatcaagag tcacctcagc tgcgcccccc tcccatcctt tcttatgaga agccactgct 480
 ttggggcgcg cggctagaaa aagtagggtg cgggtggccag gagggccct gccgcgcggg 540
 gggctgggtc tggttgagtc gctgctttcc cgagggcagc gcagggatcc ggggaagctg 600
 cggcagggag cgggcgcggg ctctgtgggt ctgaggtgta acgggggtgg gctccctccc 660
 tcggaggaca tcgtctgtgt ccaggtcaga aagtggccca ggaagggggc agtttctgtc 720
 gcgggtcccg tgggggcgcg gccgctctag aggatecc 758

<210> 92
 <211> 2152
 <212> DNA
 <213> Homo sapiens

<400> 92
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 cgcattgtgt catgtgtgtg tgtgagtggt tgtgttgggg aggaggcatg gcccttggga 180
 aggtctgtcc aggttggaaag ccacactccc tcccctcagc atggaggtgg gcgtgtgcgt 240
 ggaggcctat cgccaggagg ctgagaccca ccggcgccac atcaacagtg cttttatgac 300
 ctttgtgggt ctggacgcag atgaccagcc ccagttgctg ccctggattc ggccccagcc 360
 cggcgatggg gagcggcggt accgagaggg cagtgccaga aagaagatcc gcctggacag 420

| | | | | | | |
|------------|-------------|-------------|-------------|-------------|------------|------|
| gaagtacatc | gtgtcctgta | agcagacaga | ggtgccccct | tccgtccccct | gggaccctag | 480 |
| caaccaggtg | tacctgagct | acaataacgt | ctcctccttg | aagatgcttg | tggccaagga | 540 |
| caactgggtg | ctgtcctcgg | agatcagtc | ggtccgcctg | tacactctgg | aggatgacaa | 600 |
| gttcctctcc | ttccacatgg | agatggtggt | gcatgtggat | gcagcccagg | ccttcctgct | 660 |
| gctctcggac | ctgcgtcaga | ggccagagtg | ggacaagcac | taccggagcg | tggagctagt | 720 |
| gcagcaggta | gacgaggacg | acgccatcta | ccacgtcacc | agccctgccc | tcggaagtca | 780 |
| cacaaagccc | caggacttctg | tgatcctggc | ctcgaggcgg | aagccttggtg | acaatgggga | 840 |
| cccctatgtc | atcgcgctga | ggtcgggtcat | gctgcccaca | caccgagaga | cgccagagta | 900 |
| cagacgcgga | gagaccctct | gctcaggctt | ctgcctctgg | cgcgaggggg | accagctgac | 960 |
| caaggatatc | tactacaacc | aggccacccc | aggtgttctc | aactatgtga | ccaccaacgt | 1020 |
| ggccggcctc | tcctctgagt | tctacaccac | cttcaaggct | tgtgagcagt | ttctcttgga | 1080 |
| caaccggaa | gatctggccc | ccagcctcca | gaccctctag | atgccctcag | tggccacatc | 1140 |
| atgccactc | ccactccatc | ctgtccccaa | ggactcacat | acagtgcctg | gagaaagcca | 1200 |
| aagaccttta | tttcttctctg | cctccccgtg | ggaagcctcc | gccctgaggt | ccgctggccc | 1260 |
| accacccctg | ggtgctcagt | ttctaccaac | atgagccagc | aagtccttgt | ggtagccctg | 1320 |
| gggtagcctg | tagtagactc | gggtcctgtc | cacagcccta | gctgccagca | atgctgtcct | 1380 |
| cacagaggca | tagtcgcccc | cagctggggt | gtgctccact | gtgacgggtg | cccgggggga | 1440 |
| ggatgccagc | agcctgccta | tggctccagc | tgtgctgtgg | cccagcagca | tggcctgcat | 1500 |
| ctggaaggac | acaggttgcc | agagccctctg | gcacaactct | agcatatctg | tgagcagctg | 1560 |
| ttccctgtag | ccactgcccc | gcacctctctc | aggccagcct | ggtgccacag | tcacgtgggg | 1620 |
| gaagacctca | gccacagctg | taagcagctc | tctgccagcc | acatggccgg | ggaccgaaaa | 1680 |
| actcccgtgg | gagatttttg | ccccaaacca | cacaggccaa | tgcaagaggc | caaggctgga | 1740 |
| gagggctggc | agcaaggcca | gggatggccg | gagggctgcg | ggctccgcta | tttgcaaata | 1800 |
| gatgccccc | tgtccgggat | gtgtggccag | ctgctgcagg | caggactcca | gcgtcaggat | 1860 |
| ggtgccactt | ggagtatgaa | caatgggcac | ggggttttca | gccacagttc | cctcgaggcc | 1920 |
| agtgttcagc | aggatcatgc | cttctgtgtc | tggaagaggc | ggcagaggca | acagtgttta | 1980 |
| ggatttgggt | tatcataagg | tgtaagagt | cccttggttaa | aggggcagtg | ggagttatgg | 2040 |
| ggtcatcaag | gaccttgctt | ctctggaatc | tgtcaaccca | gttttgggct | ccaggtggat | 2100 |
| gggttgcttt | ataaatgtgc | ctggtgcatg | agaaaaaaaa | aaaaaaaaaa | gg | 2152 |

<210> 93
 <211> 758
 <212> DNA
 <213> Homo sapiens

| | | | | | | |
|------------|-------------|-------------|------------|-------------|-------------|-----|
| <400> 93 | | | | | | |
| ggcacgaggt | gtgggtgggc | aaggccaggg | ccactgccag | gtgggggtccg | tggccctgag | 60 |
| ccccagctc | tatgcacccc | ccacctgggg | tctggttctt | ccatctccac | accccttgga | 120 |
| ggggcttctg | tctccccctg | cccccttcgat | cgcaggaggc | agtgcctggc | cggggtcgca | 180 |
| ggcacctgtc | accccagctc | ctcactcctc | acccactcac | atccagtccg | tttgtaaaat | 240 |
| acaccagga | tgagacctgc | acgcagtggc | ttacagcagc | acgatttggtg | acagcccagag | 300 |
| gcggagaaca | ccgaacaccc | agtgaagggtg | aggggatcag | cacggcgccg | ccaccgtgct | 360 |
| ggaacgagac | tcagccacaa | ggaggtgcca | agctctgacc | caggccacag | tgcggtatgca | 420 |
| ccttgaggat | gtcacgctca | gtgagagaca | ccagacacag | aagggtacgc | tgtgatccca | 480 |
| cttctatgaa | atgtccagga | cagaccaatc | cacagaatca | gggagaggat | tcgtgggtgc | 540 |
| cgggactggg | gaggggggacc | tgggggtgac | taggtgacat | aatggggaca | gggctgcctt | 600 |
| ctgggtgat | agaatgttct | ggaatcagat | gggatggctg | cacggcggtg | tgaaggctact | 660 |
| gaacggcacc | tcactgtaag | acggtagatt | ttgtatttta | ccacaataaa | caaaacaaaa | 720 |
| caaaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | aaaaaaaa | | | 758 |

<210> 94
 <211> 1116
 <212> DNA
 <213> Homo sapiens

| | | | | | | |
|-------------|------------|-------------|-------------|-------------|------------|-----|
| <400> 94 | | | | | | |
| gcaggagagt | agttatagac | cctcaagaga | aaccacagtga | ggagccccctt | ggggaccgaa | 60 |
| ggactgtcat | tgacaaatgc | tctccacccc | tagagttctt | ggatgactct | gactctcatt | 120 |
| tagaaatcca | aaagcataaa | gataggagg | tggtgatgga | gcacccctct | tctggaagtg | 180 |
| actggctctga | tggtgaggag | atctccacag | tcagattctc | tcaggaggaa | cctgtctccc | 240 |
| tgaaaccttc | agccgttccg | gagccttctt | ccttcaccac | cgactatgtc | atgtaccctc | 300 |
| ctcatttgta | cagtagtctt | tgggtgtgact | acgccagcta | ttggaccagc | agccccaagc | 360 |
| cttctagcta | cccctccaca | ggcagcagca | gcaacgatgc | agccaggtt | gggaagagca | 420 |
| gccggagccg | catgagtgat | tattccccca | actctacagg | gagtgtccaa | aacacctcca | 480 |
| gagacatgga | ggcctcagag | gaaggctgg | cccagaattc | tcgttcattt | cgcttctcca | 540 |
| gaagctcaga | agaaagagag | gtgaaggaga | aaagaacatt | ccaagaggag | atgcctccgc | 600 |

| | | | | | | |
|-------------|------------|-------------|-------------|------------|------------|------|
| gtccttgtgg | aggacacgca | tccagctccc | tgcacaaagag | ccacctggag | ccaagcctag | 660 |
| aggagggcctt | cattgacact | cattgtcacc | tgacatgct | ctattccaag | ctatctttcc | 720 |
| aaggacacctt | tacaaagttc | agaaaaat | acagcagctc | cttccctaag | gaatttcagg | 780 |
| gctgcatctc | tgacttctgt | gttagaggag | gaaaagcgga | gatgacatgg | aagtctccaa | 840 |
| gcctgtgcca | tccacctgcc | aaggaaaagc | acaagggtgt | atctactttt | ctctctagga | 900 |
| tttagattat | catttatgtg | ctgttgacaca | gtgaaacctc | acctgtgtgg | gcgtgaaagc | 960 |
| tgattggcat | tgtttttgat | tcagcttttt | ggatggctaa | ttgttttcac | tgtgctgtgg | 1020 |
| gaatgcctct | gtattttttc | ccctcttttg | ccatcttttt | ctgaaaataa | agtgatggat | 1080 |
| cctctagcca | aaaaaaaaa | aaaaaaaaa | aaaagg | | | 1116 |

<210> 95
 <211> 724
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (1)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (2)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (3)
 <223> n equals a,t,g, or c

| | | | | | | |
|------------|------------|------------|------------|------------|-------------|-----|
| <400> 95 | | | | | | |
| nnnggcacga | gatcttttgc | aagccttaag | gcaccctaag | gctgtggcat | ttggagaaat | 60 |
| gggcttggat | tactcttaca | agtgcaccac | gcctgtccca | gaacagcaca | aggtatttga | 120 |
| gagacagctg | cagctggctg | tgtctctaaa | gaagcccttg | gtgatccact | gccgagaagc | 180 |
| tgatgaagat | ctgctagaaa | tcataaaaaa | gtttgtgccc | cctgactaca | agatccatag | 240 |
| gcattgcttc | accggcagct | accgggtcat | tgagcccttg | ctgaagtact | ttcccaacat | 300 |
| gtctgtgggc | ttcacggcag | tgctgacata | ctcctctgcc | tgggaggccc | gggaagcctt | 360 |
| gaggcagatc | ccactggaga | gaatcatcgt | ggaaacggat | gctccctatt | tcctccctcg | 420 |
| ccaggttccc | aaaagccttt | gccagtatgc | ccaccggggc | ctggccttgc | atacgggtccg | 480 |
| agagattgcc | agagtcaaa | atcagccact | ctccctcacc | ttggctgcct | tgctgtgagaa | 540 |
| caccagtgcg | ctctacagtc | tttaagcaga | gaaggtacag | tcctcgggag | tctcctagaa | 600 |
| aaggtcgtaa | aactcacatt | ctgtattttt | taaaaaccag | gacaagtctt | ttgttgcat | 660 |
| ttgttaatgt | aaagaatata | aacatagtat | gagcattaaa | aaaaaaaaa | aaaaaaaaa | 720 |
| aaaa | | | | | | 724 |

<210> 96
 <211> 636
 <212> DNA
 <213> Homo sapiens

| | | | | | | |
|------------|------------|-------------|-------------|------------|-------------|-----|
| <400> 96 | | | | | | |
| ccttgccaac | tctgcctctt | cccccgctga | ctgggggtatc | agtttatggg | gccctgcagg | 60 |
| aagaccctct | tgttcctgtg | gggtgggaagc | ctctgcagag | atgtgggcag | ctggtcaggga | 120 |
| tggccattcg | ggctcagcac | agcaacgcag | cccagactca | gactggggaa | gcaaacaggg | 180 |
| gctggacagg | ccaggagagc | ctgtcggaca | gtgatcctga | gatgtgggag | ttgtgcagaa | 240 |
| gggagaagga | caggcagtg | cgtggcctgg | agctcattgc | ctyagagaa | ttctgcagcc | 300 |
| gagctgcgct | ggaggccctg | gggtcctgtc | tgaacaacaa | gtactcggag | ggttatcctg | 360 |
| gcaagagata | ctatggggga | gcagagggtg | tggatgaaat | tgagctgctg | tgccagcgcc | 420 |
| gggccttgga | agcctttgac | ctggatcctg | cacagtgggg | agtcaatgtc | cagccctact | 480 |
| ccgggtcccc | agccaacctg | gccgtttaca | cagcccttct | gcaacctcac | gaccggatca | 540 |
| tggggctgga | cctgcccgat | ggggggccatc | tcacccacgg | ctacatgtct | gacgtcaagc | 600 |
| ggatatcagc | cacgtccatc | ttcttcgagt | ctatgc | | | 636 |

<210> 97
 <211> 1204
 <212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (1187)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1196)

<223> n equals a,t,g, or c

<400> 97

| | | | | | | |
|-------------|------------|-------------|-------------|-------------|------------|------|
| ggcacgagag | agcctggggc | cagagggcca | gacagccaca | gagctcctgg | cgtgggcaag | 60 |
| gctggccaag | gatggcgacg | cccagkggcc | tgggggccct | gctcctgctc | ctcctgctcc | 120 |
| cgacctcagg | tcaggaaaag | cccaccgaag | ggccaagaaa | cacctgcctg | gggagcaaca | 180 |
| acatgtacga | catcttcaac | ttgaatgaca | aggctttgtg | cttcaccaag | tgcaggcagt | 240 |
| cgggcagcga | ctcctgcaat | gtggaaaact | tgcagagata | ctggctaaac | tacgaggccc | 300 |
| atctgatgaa | ggaaggtttg | acgcagaagg | tgaacacgcc | tttcctgaag | gctttggtcc | 360 |
| agaacctcag | caccaacact | gcagaagact | tctattttct | tctggagccc | tctcagggtc | 420 |
| cgaggcaggt | gatgaaggac | gaggacaagc | cccctgacag | agtgcgactt | cccaagagcc | 480 |
| tttttcgac | cctgccaggc | aacagggtct | tgggtccgct | ggccgtcacc | attctggaca | 540 |
| ttgggtccagg | gactctcttc | aagggtgagga | ctcagggaag | ctccaaggtt | aagtgtcagg | 600 |
| tcctctgggg | gctccatgcc | acagtttgct | gtcactggag | cctgccgagg | gatccaatgg | 660 |
| ggacagagca | ggcagtgagc | ctcttagtgt | ttctaattgca | gcccgtggcc | atctcagaca | 720 |
| cctgtcacta | gagtctatgg | tcttcagact | cacactggtc | acacgctctc | agatgtttga | 780 |
| ccccacaca | tgagtgcctt | ttggcttgct | tatgtgtcct | gtgggtgctc | gtgtgctctg | 840 |
| tgtgtcctcg | tgcatgcaca | aacatgcaca | tccttttcta | ttcttgtgca | cgcacaagcc | 900 |
| catgtactca | gctgtgatca | tatccacacg | agcaagtgtg | cccattgccct | tgcatatgtg | 960 |
| tataccagg | atgtgcaccc | agaggtgtgc | atccactcct | gtgcagacgt | gtgtaccctt | 1020 |
| gagggctagt | gtgtccccc | caccagcctc | ctttctaccg | aatgcacact | cacgctaaga | 1080 |
| ccctcagggg | cacgctatcc | tccccgctga | cttccatttc | ttggctgatc | ttggccccat | 1140 |
| gccccctttt | msctttttaa | gggtttttaa | aaaggggaagg | gggggggnccc | aaaggnaaag | 1200 |
| ggggg | | | | | | 1204 |

<210> 98

<211> 1117

<212> DNA

<213> Homo sapiens

<400> 98

| | | | | | | |
|-------------|-------------|-------------|------------|------------|-------------|------|
| gcgaggacca | gctgwcctgg | ttcgctgccc | tgggtcaagt | cctgcccgtc | ctctgcctgg | 60 |
| ctgggttcct | gtgggtcatg | tccccaagcg | ggggctacac | ccagctcctc | cagggagccc | 120 |
| ttgtgtgctc | ggctgtgggg | gacgcttgcc | tcactctggc | ggcagccttc | gtccctggca | 180 |
| tggccgcctt | tgccaccgcc | cacctcctct | acgtctgggc | cttcggcttc | tctccccctg | 240 |
| agcccggcct | gctgctgctc | atcatcctgg | cccctggccc | ctacctcagc | cttgtgctcc | 300 |
| agcacctcga | gccggatatg | gtcctgcccg | tggcagccta | tgggtgatc | ctgatggcca | 360 |
| tgtgtggcg | cggcctggcc | cagggcggga | gtgccggctg | gggcgcgctg | ctcttcacgc | 420 |
| tctctgatgg | cgtgctggcc | tgggacacct | tcgcccagcc | cctgccccat | gcccrcctgg | 480 |
| tsatcatgac | cacctactat | gctgcccagc | tcctcatcac | actgtcagcc | ctcaggagcc | 540 |
| cggtgcccac | gactgactga | ctagggagct | tgaagggccg | gtgttcaggc | cctctcctcc | 600 |
| tgcaaggacc | tgggcctccc | agcccagccc | mgcctgagaa | ataccctcag | cagcgaagct | 660 |
| tcctgacgcc | tgtctgcagg | cgygctgccc | gccgtcgctt | ctggctgaag | acgtttgagg | 720 |
| acgattttcg | gaattccaag | tccactactg | ggttccagct | gccttcccc | ggttctgact | 780 |
| ccagatccct | ggctcctcag | ccaggcccac | atggagccct | cccagccacc | agcctgcctc | 840 |
| catgttcaact | gtcggcccca | cagcctgccc | gccccctgct | gctgctctga | atccgttttc | 900 |
| cctgtgggtg | tggaaaccgta | gatgttgctg | ttaccgtagg | agaggcctcg | gggaggggtca | 960 |
| tcatttgtgat | aaaccatcgc | gggttaatgac | agcagaaggt | tctttgtcgc | tccccatgga | 1020 |
| ccaggcctgg | tgcccagtg | gaccctccat | ggccctctgg | tggggggatt | cgggggggata | 1080 |
| aagtgaggat | tgtgcagaac | tgaaaaaaaaa | aaaaaaaaa | | | 1117 |

<210> 99

<211> 1092

<212> DNA

<213> Homo sapiens

```

<400> 99
cgaattctgc tcagctcgct ttggcagctt ggtgggcggt gggcgcggtt ggccggagggc 60
attgaagctg ctggcccagc atgtggtgctg cgagcccagt tgctgtggtg gcctttttgctg 120
ccgggctttt ggtctctcac ccggtgctga cgcagggcca ggaggccggg gggcgggccag 180
ggcccgactg tgaagtatgt aaagaattct tgaaccgatt ctacaagtca ctgatagaca 240
gaggagttaa cttttcgctg gacactatag agaaagaatt gatcagtttt tgcttggaca 300
ccaaaggaaa agaaaaccgc ctgtgctatt atctaggagc cacaaaagac gcagccacaa 360
agatcctaag tgaagtcact cgcccaatga gtgtgcatat gcctgcaatg aagattttgtg 420
agaagctgaa gaagttggat agccagatct gtgagctgaa atatgaaaaa aactgggact 480
tggcatcagt tgacctgcgg aagatgagag tggcagagct gaagcagatc ctgcatagct 540
ggggggagga gtgcagggcc tgtgcagaaa aaactgacta tgtgaatctc attcaagagc 600
tggcccccga gtatgcagcg acacacccca aaacagagct ctgatctcca atgccagcac 660
atttgtgact tgtaattaga gagaaaagtg actctctagg atatggacat gttgattaag 720
gataactggg aatgcatcat atttggctct atgctttttg tgttggattt attcctcaga 780
attttgttac gtgggtttat gagtgaact aatactactg ataacttaca tttgcagtgt 840
acaaaagct aaaagttcct ttctcataag tttcttggaa tgactatgcc agttttcatt 900
gcctgtctcc taaaagtgcac ctactgacaa attgatggag taaattgatt ccaagaaaga 960
agaaggcatt cagagactcc tctctggatg caattttaaa atatattgga ctaaaacaaa 1020
agacacaaca gtcagcttat ctaatgcaca acttcaatcc caaatacaga atcaaaagtt 1080
tttttcaagt ga 1092

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<210> 100

<211> 1450

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (1374)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1415)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1418)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1426)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1439)

<223> n equals a,t,g, or c

<400> 100

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atgaacgacc gaggccaggg agtcctctcc ttgggcctct gcatccccc atccttggct 120
ctggggtagg cccaggaggg agacaccccc aaccctatc cggctgtgctc tggagaaaag 180
agactgccct tccatgcccc tgagtgaggg gcctggggcc caggctgcct gtgttcccca 240
agggcaaggg tctctctggt gaggaggagg ggcctgtcag ccacaacttc tttcctcctg 300
agcgcccat ctccctctct gcaccctgca attcccaccc ctccgtattt atttccctgg 360
tcccgcgcag agtccctcct tgtctgtctc cgggattcag gcctccctcc ctgacatgga 420
gagtaacctg tctggcctgg tgccctgctg cgggctgggt cctgcgctgc cacctgctgt 480
gaccctgggg ctgacagctg cctacaccac cctgtatgcc ctgctcttct tctccgtcta 540
tgcccagctc tggctggtgc ttctgtatgg gcacaagcgt ctgagctatc agacgggtgtt 600
cctggccctc tgtctgctct ggccgcctt gcgtaccacc ctcttctcct tctacttccg 660
agatactccc cgcgccaacc gcctggggcc cttgcccttc tggcttctct actgctgccc 720
cgtctgcctg cagttcttca ccttgacgct tatgaacctc tactttgccc aggtgggtgtt 780
caaggccaag gtgaagcgtc ggccggagat gagccgaggc ttgctcgctg tccgaggggc 840

```

| | | | | | | |
|-------------|------------|-------------|------------|-------------|------------|------|
| ctttgtgggg | gcctcgctgc | tctttctgct | ggtgaacgtg | ctgtgtgctg | tgctctccca | 900 |
| tgggcgcggg | gcacagccct | gggcccctgct | gcttgccgc | gtcctgggtga | gcgactccct | 960 |
| gttcgtcatc | tgcgcgctgt | ctcttgctgc | ctgcctctgc | ctcgtcgcca | ggcgggcgcc | 1020 |
| ctccactagc | atctacctgg | aggccaaggg | gaccagtgtg | tgccaggcgg | ccgcgatggg | 1080 |
| tggcgccatg | gtcctgctct | atgccagccg | ggcctgctac | aacctgacag | cactggcctt | 1140 |
| ggccccccag | agcgggctgg | acaccttcga | ttacgactgg | tacaatgtgt | ctgaccaggc | 1200 |
| ggacctgggtg | aatgacctgg | ggaacaaagg | ctacctggta | tttggcctca | tcctcttcgt | 1260 |
| gtgggagcta | ctgcccacca | ccctgctggg | gggcttcttc | cgggtgcacc | ggccccca | 1320 |
| ggacctgagc | accagccaca | ttcctcaatg | ggcaaggctc | tttgscctcty | gggncctact | 1380 |
| tcttttgacc | ggggcttggg | cacttgkgaa | aratnrangg | gcttgnttct | tggaaccna | 1440 |
| aaccgggtg | | | | | | 1450 |

<210> 101
 <211> 764
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (636)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (641)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (733)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (743)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (764)
 <223> n equals a,t,g, or c

| | | | | | | |
|------------|------------|-------------|------------|------------|------------|-----|
| <400> 101 | | | | | | |
| tttctgctgg | tgaacgtgct | gtgtgctgtg | ctctcccatc | ggcgccgggc | acagccctgg | 60 |
| gccctgctgc | ttgtccgcgt | cctgggtgagc | gactccctgt | tcgtcatctg | cgcgctgtct | 120 |
| cttgtctgct | gcctctgcct | cgctcgccagg | cgggcgcctt | ccactagcat | ctacctggag | 180 |
| gccaagggga | ccagtgtgtg | ccaggcggcc | gcgatgggtg | gcgccatggt | cctgctctat | 240 |
| gccagccggg | cctgctacaa | cctgacagca | ctggccttgg | ccccccagag | ccggctggac | 300 |
| accttcgatt | acgactggta | caatgtgtct | gaccaggcgg | acctggtgaa | tgacctgggg | 360 |
| aacaaaggct | acctggtatt | tggcctcatc | ctcttcgtgt | gggagctact | gcccaccacc | 420 |
| ctgctggtgk | gcttcttccg | ggtgcaccgg | ccccacagg | acctgagcac | cagccacatc | 480 |
| ctcaatgggc | aggtctttgc | ctctcggtcc | tacttctttg | accgggctgg | gcactgtgaa | 540 |
| gatgagggct | gctcctggga | gcacagccgg | ggtgagagca | ccagtatgtc | gggcagtcta | 600 |
| ggctctggga | gctggtatgg | tgccatcggg | cgtganccgg | nctggtatgg | gggcagccag | 660 |
| acgaagacca | ctcctctgtc | tctccagtgc | agacagcgga | cacacagctt | atcaccaaac | 720 |
| ggtcctctcc | aanaaccagc | cancctacta | gctggcagtg | tgcn | | 764 |

<210> 102
 <211> 880
 <212> DNA
 <213> Homo sapiens

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 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (805)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (877)
 <223> n equals a,t,g, or c

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 aattaacagt gagtggnggg ttttaactga tggaaaccgat tccatcgact ttagcctgga 780
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 <211> 1321
 <212> DNA
 <213> Homo sapiens

<400> 103
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 ctgctggagc tcaggcagct gcagcccatg ttcacgtgc aggtgggtccc gctccaccga 480
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 a 1321

<210> 104
 <211> 1558
 <212> DNA
 <213> Homo sapiens

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<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1550)

<223> n equals a,t,g, or c

<400> 104

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| acactccctg | aatgctgtg | tggtgggtttc | cctggaggat | tcttgctgca | ggccagggtcc | 120 |
| cgtattctcc | acactcacca | caagtggctg | gggtgtgactt | gacacgggtgt | gaaagtggag | 180 |
| gggcgcgagc | actcagtatc | cagcgagcag | cattgggtggt | cctagaaaaat | tactacaaaag | 240 |
| atttcaccat | ctataaccca | aacctcctaa | cagcctccaa | attccgagca | gccaagcata | 300 |
| tggccgggct | gaaagtctac | aatgtagatg | gccccagtaa | caatgccact | ggccagtccc | 360 |
| gggcatgat | tgctgcagct | gctcggcgca | gggactcaag | ccacaacgag | ttgtattatg | 420 |
| aagaggccga | acatgaacgg | cgagtaaaga | agcggaagc | aaggctgggtg | gttgacagtgg | 480 |
| aagaggcctt | catccacatt | cagcgtctcc | aggctgagga | gcagcagaaa | gccccagggg | 540 |
| aggtagatga | ccctagggag | gccgcccagg | ccattttccc | ctccatggcc | agggtctctc | 600 |
| agaagtacct | gcgcatac | cggcagcaga | actaccacag | catggagagc | atcctgcagc | 660 |
| acctggcctt | ctgcatcacc | aacggcatga | cccccaaggc | cttcctagaa | cggtacctca | 720 |
| gtgcggggcc | caccctgcaa | tatgacaagg | accgctggct | ctctacacag | tggaggcttg | 780 |
| tcagtgatga | ggctgtgact | aatggattac | gggatggaat | tgtgttcgtc | cttaagtgtc | 840 |
| tggacttcag | cctcgtagtc | aatgtgaaga | aaattccatt | catcatactc | tctgaagagt | 900 |
| tcatagacct | caaattctcac | aaatttgctc | ttcgcttaca | gtctgagaca | tccgtttaaa | 960 |
| agttctatat | ttgtggcttt | attaaaaaaa | aaaraaaaaat | atatagagag | atatatatct | 1020 |
| atgccagagg | gggtgtctttt | ttaaaaattc | ttcttcattg | ctgactgaaa | ctggcagatg | 1080 |
| attgaccagt | atcctttgac | catctgcact | ttattttggaa | ggaagcaggg | gctgtccacc | 1140 |
| ctgaaaaaga | gtgactgatg | acatctgact | tttgtcgatg | ggacttctca | agaagccatt | 1200 |
| ccttgaggct | tctgttacag | ctgtaaacca | aagtggagct | gggtgcttctt | gggagcctcg | 1260 |
| ccttacaact | agttcctgcc | tttcgtccag | taccaagtcc | cccgttgctt | ctggtcagcc | 1320 |
| cacttgtaga | cttcacgggg | acacatcttt | attctgtttc | aggaaaccag | tcacracacg | 1380 |
| tccacatatg | tattttgtgta | tgttaatgtc | cagtatcaca | tcacccatga | aagtcgtggg | 1440 |
| cagttcarga | gatacctgsc | ttcgtctttg | ktctttgttg | ccttaggttc | ttcagagaaa | 1500 |
| gatcmcaaca | aaaaatgtac | mctgtcgttt | acagctawaa | gngatttgan | ttgttttt | 1558 |

<210> 105

<211> 2079

<212> DNA

<213> Homo sapiens

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<221> SITE

<222> (1603)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1918)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1920)

<223> n equals a,t,g, or c

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<221> SITE

<222> (1976)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1980)

<223> n equals a,t,g, or c

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<221> SITE
 <222> (2017)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (2020)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (2027)
 <223> n equals a,t,g, or c

<400> 105

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| cacgcgtccg | attcatagca | gtatggactc | atggatacat | attttattct | gtgggcaata | 120 |
| cccgttacta | tcattatttg | tttttcttgg | cttgaatatt | ctcagacttg | ggctttgggt | 180 |
| gcttcttgta | gtttgccgca | atgccctttt | gatgtgatgc | tatcattatt | tttagtacat | 240 |
| ccttactttc | caacagtatg | ggatcatctt | tgttttcccc | atcccagtc | tgaaagtagc | 300 |
| cctttctcca | agtgttctac | ggttgcttgg | ttggagaatg | gtgcatagga | accaagatct | 360 |
| gagtgcaagg | gtgctcttca | ctggtgggat | gtcattgctt | ctgggtgtgt | tggagccagc | 420 |
| aaatatatat | atgtacacta | attcatgcat | gcacacattt | gcatttattt | atacatctat | 480 |
| ccatctgcgt | gtgtatagct | gtgtgtatat | gtgttaccat | gagttaatac | caattactct | 540 |
| gatttcaatc | caacacaatg | ggttctttct | aattattttt | aatttctctc | aaaatcactt | 600 |
| cttctggktc | ttccagaaaa | tgagctcttc | acctagctta | agaatgtaga | gatgycgtgk | 660 |
| atgggtgggc | aggttgttca | ctgtccaagg | gtgttccagc | tgaggagagc | gatgggagct | 720 |
| gaaagcatcc | atgctctact | ccctaagctc | tgactcttaa | catgtgctct | gggtccacca | 780 |
| gagtaaggga | tgccctcttt | tcacttgtgc | aaatgcactg | ggtgagctag | caacagacct | 840 |
| ggtcgactgc | tgtctcgga | tatttttgcg | tttacttgtg | aaacacccag | gcttgggctg | 900 |
| gattccccca | tgagagatt | gtgagctgag | gatttgagt | cgaggagtat | tttgggatgt | 960 |
| gattccagga | acctcccaga | gagaagcagt | ggggagtcag | gcaggaaaga | aagcatgcgt | 1020 |
| cagggagctg | gktactactg | ggccaccgag | gctccatccc | agtaagggaac | cctggaagac | 1080 |
| gggaggaacg | caccttgga | ttgcttycct | aagggatcaa | cttcagttgg | tcgccactca | 1140 |
| aggctcctcc | tgaggggagc | aggcacagag | tccctggcac | ttctggccct | gagtgcccg | 1200 |
| gggatgagtg | cgtgacattg | acggcttctg | ctgtcctctg | tctcctgctt | tccccgtggg | 1260 |
| atgaactagc | ttgagaggca | caagattcct | gagcaggcag | agggaactctg | taggagtctc | 1320 |
| agagctcctg | aggctgcacc | ctcgccctgg | agccccgtga | aatcttcaat | tttgggtttt | 1380 |
| atgagcttca | caaaccttcc | aggggcctct | ccggctccgg | atgggggtgcg | ttggaggcct | 1440 |
| ggtgcccacg | tgtctcctgg | gccctccacc | tgtgccccgc | ctgtttgcac | agtgtgctg | 1500 |
| agctgagcac | ctgagtttgc | tctttgaatc | aagtgkttaa | ctcactcacg | gtaatagtgg | 1560 |
| ctgataattc | ttgagctaac | acaccttcta | ctttgcgsc | tanccttgkt | tgcccttcag | 1620 |
| ccctggkttta | wtatcttcca | tcggatgaag | cttargagca | ccagcgctgc | ctarggaaac | 1680 |
| cctggcccyt | ccttccctgg | gatcatctgg | gtcccccagg | gctcaggctt | tacaaccctt | 1740 |
| gctgcttgg | taccacctc | ccacctgggg | cccctgacag | atcaggggac | aagcagatag | 1800 |
| agggctcacc | agtgcaagtc | caagtgtatg | ctgccggcsg | gccggagcag | agtgagtc | 1860 |
| gatttggctt | tttataatca | ttcaggtgcc | arggtgggca | cgccgtcctg | gggtcatncn | 1920 |
| ttccagcgaa | gggctcacia | tcataagcct | ggcaccagc | aagtaaattc | aagcanggan | 1980 |
| gggttttaaat | tttccttccc | ttatggggaa | tcaagcnaa | gggcaanctt | ggccttaaag | 2040 |
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<210> 106
 <211> 3144
 <212> DNA
 <213> Homo sapiens

<220>
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 <222> (3135)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (3138)
 <223> n equals a,t,g, or c

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<210> 107
<211> 843
<212> DNA
<213> Homo sapiens

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<220>
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<223> n equals a,t,g, or c

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<220>

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<221> SITE
 <222> (2)
 <223> n equals a,t,g, or c

<220>
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 <222> (841)
 <223> n equals a,t,g, or c

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 gggccggagc agagtgaagc agatttggtt ttttataatc atccaggtgc caggggtgggc 180
 acgcgtcctg ggatcatcctt ccagcagagg ctcacatcat agcctgtcac cagcagtaat 240
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 tttggaagtt ggtaatttca ttgggaaggg ccttctgggt ttttcaattt tgggggaagt 780
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 ngg 843

<210> 108
 <211> 613
 <212> DNA
 <213> Homo sapiens

<400> 108
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 aatcttagtt tttatatagt ccaactcatg tactctgctt ccgtcattaa gaattcatag 180
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 tggtttgttt ctttagacag tcttgctatg ttgccaggc tggagtgcag tggcacaatc 300
 acagctcact gcaacctctg tctcccggtt tcaagagatt cttctgcctc aacctccga 360
 gtagctggga ttacaggcac atggcaacat gcccctgggt aatttttgta tttttagtag 420
 agatggagtt tcgcatggtt ggccaggctg gtcttgact cctgacctca agtgatctgc 480
 ctgccttggc cttccaaagt gctgggatta caggactgag ccaccacgcc tggccagggc 540
 gttttcttaa aaaagtgatt gaaatctgct catgccctgt gccacgtggg tctcacgcag 600
 gtctgttctc tgc 613

<210> 109
 <211> 945

<212> DNA
<213> Homo sapiens

<400> 109
 gggcagcaga cctgcttcat ttgcgcagtc tgccatgtga atctggaggg gcagccgttc 60
 tactccaaga aggacagacc cctgtgcaag aagcacgcac acaccatcaa cttgtaggcg 120
 gccaaggccg cctgtgctga cgaggcccgg agctgtctct gctgctggca acaaaggatt 180
 cgaggaggctg atgtttcttc tgaggggaat ggggagagag aggaagcgac tgagcccttt 240
 ggaagtataa ttttaggttt tttcttctgt acacagatcg tgcatttgca tagttcagac 300
 taggagccaa atgaagactc aaaaccaagc tagttattaa tccaagactg gaattgtact 360
 tcagacattt agagcagaat tccaagaact caaaagtga aagcaacaag cagctttccc 420
 aaagcgatac acttgctttg gtcaccagag gaggacagag cttagagcag ctgtggagaa 480
 tctgaagcat tctgaggagt tcttaagcgc tcccctggca aacaaattga agtgccaaac 540
 agcactcgct gcagggtatt tttagagtca tagctgagag cttgttagct aagaccatt 600
 gggcttttct caccaaaaaa ggaagtgtta ttccattact agcgtcatgg agctacctct 660
 gcgcatcaga cttcagacct tgaacaaact taaaaccttc ttgggagccc ggacgtccaa 720
 agagatgtct tctgggagcc actgggcaat tgccagggt ccaggaaggg ctctggctca 780
 gggtgcagac agctgagaaa agatggccct gtcagccacc ctctctcagt ctgaaacatc 840
 caacatcccc agaaggctta gctccttttt gaattgtgat gggaaagtag agttgggttt 900
 ttctctgtgc cgaattcgat atcaagctta tcgataccgt cgacc 945

<210> 110
<211> 450
<212> DNA
<213> Homo sapiens

<400> 110
 gaggcctgag agccgggcaa gggctgtcgc acatgcgcct tgagggaaga tggcacctgc 60
 cggctgtctgc tgctgtctgc gcttctgtggg cggcgctgtg gccgcgcgkg gcgcgcgccg 120
 gcgtgtcctg ctgctgtctgc tgctgggggw cctgtctcgc cggctgcggc caggcgccct 180
 ggccaccgag cactactcgc cgctcgccct gctcaagcag gagctgcakc accggcagca 240
 gcaggaggcc cgcscgggcg gcggcggtg cagcccgag tccggggact ggggggacca 300
 gtactctgcc gagtgcgcg agtcattcct tttgmacttc catgactcag actgcgaacc 360
 ccaaggatca tcaccctgtg actccttgct ttccctcaac actgcgaaga ttctgagcca 420
 ggccaagtct attgcagaac agaagagatt 450

<210> 111
<211> 773
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (731)
<223> n equals a,t,g, or c

<400> 111
 tggaagctaa aacacagggg gctggtgggt tgggtggggg cagataatga tatgcataca 60
 aattagaggg tctatgcaaa tgagcattgc tgacgtgtgg ctggaggga tcttagttc 120
 ctaggattct aggatatggg tttcgacccc agaggtgaat gtattgttat tattgttttg 180
 ttgttggtgt gaatgacaag tcaaaatttg tgggttattg ttgttatcgc caatagtatt 240
 cttgtcattg ttgcacagta cagagatgaa ggaacagat tttgcaatca gatgatcctg 300
 ggttctgagt ccactctgcc actcaccagc tatatgacct ccagcaattt ccatcacctc 360
 tcaatgcttc agtttcccca tcggcaagat ggttgtgggg ggagaggaa aacagtacag 420
 attcaccatc ccaaattcaa aatgctccaa aatctasgcc ggscgtgggt gctcatacct 480
 gtaatcccag cactttgrga ggtcaaagwg gacggataac ctgaggtcag gagctccaga 540
 ccakcctgrc caacatggcg aaaccccatc tctactaaaa atacaaaaaa ttacctgggt 600
 gtggtggggg gcacctgtaa ccccagctac tcgggagggt gaggcaggaa ccctggaggt 660
 tgaggttgca gtgagctgag atcacaccac tgcactccag cctgggtgac agagcaaggc 720
 tcccatctca naaaacaaaa aaacatgctc caaatctga aactctttga gcc 773

<210> 112
<211> 830
<212> DNA
<213> Homo sapiens

<220>
 <221> SITE
 <222> (15)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (51)
 <223> n equals a,t,g, or c

<400> 112
 caaaaaacat gttcnaaaat ctgaaacttt ttggagccca agtgtgatgc nacaagtggg 60
 aaattccaca actcatcacr tgtgatagat tgcagtggaa atgcaggcac acaccacgaa 120
 gtttactcag catcctcaaa ggaaatcccc gtcagtagct atatatcatt ttctcacatg 180
 ccagataggt atctctcatc ttttactgtt aggtacttct gtgttgaata ggtggaggaa 240
 aatgattgct ggtagtagt atataaattc agagtcagga aggatgggtga tgcgggctgg 300
 gtgcagtggc tcatgcctgt aattccaatg tgatacccta ccttgtgttt aacgtgattg 360
 acyctccctt agctgagarr gccagrcaga ctcyattttg gctycttcry ttgcagtcyc 420
 tcacccaccc cccttctca aggacttaag ctgactccca gcacatccaa gaatgcgatt 480
 actgataaga tactgtgaca agctatatcc acarttccca ggaattcgtc yggttgatag 540
 cacccaaagc ccccgctct atcaccttgt gatasattta aagcccctgc acctggaact 600
 gtttgtttty ctkttaccat ttatcttttt maytttcttg cctgttttgc ttcyrtaaaa 660
 ttgcttcagc tckgctccct cytccccctc taaaccaagg tataaaaaga aacctagccc 720
 cttcttyggg gtgagagaat tttgagcgt agcrtctct cagtcgccgg ctaataaagg 780
 actcctkaat tagtctaaaa aaaaaaaaaa aaaaaaaaaa aaaaactcga 830

<210> 113
 <211> 646
 <212> DNA
 <213> Homo sapiens

<400> 113
 cttgtgagca ggtgaagctc atctaactag gcatttctat gatgtggctg cttttaacaa 60
 caacttgttt gatctgtgga actttaaatg ctgggtggatt ccttgatttg gaaaatgaag 120
 tgaatcctga ggtgtggatg aatactagtg aaatcatcat ctacaatggc taccacagtg 180
 aagagtatga agtcaccact gaagatgggt atatactcct tgtcaacaga attccttatg 240
 ggcgaaacaa tgctaggagc acagggtccc ggccagttgt gtatatgcag catgccctgt 300
 ttgcagacaa tgcctactgg cttgagaatt atgctaattg aagccttgga ttcttcttag 360
 cagatgcagg ttatgatgta tggatgggaa acagtcgggg aaacacttgg tcaagaagac 420
 acaaaacact ctacagagaca gatgagaaat tctgggcctt tagttttgat gaaatggcca 480
 aatatgatct ccaggagta atagacttca ttgtaaataa aactgggtcag gagaaattgk 540
 atttcattgg acattcactt ggcactacaa tagggtttgt agccttttca ccattgcctga 600
 actggcacaa agaatcaaaa tgaattttgc cttgggtcct acgate 646

<210> 114
 <211> 739
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (19)
 <223> n equals a,t,g, or c

<400> 114
 cctattggga aagctggtnc gcctgcaggt accggtccgg aattcccggg tcgacccacg 60
 cgtccgcaaa atacctgagc ccaggtaatt tataaagcaa tgaggtttat ttggcttatg 120
 tttctgcagg ctgtacaagc ttctggtaag ggcctcagga agcttcaca cacggtggaa 180
 gatgaagggg agccagaatg tgcagattac atggtgagag agtgggaagca agagagaggg 240
 gcaggagggg ccaggatctt ttcaacaatc agctcatgga tgagcacagt ggctcatgcc 300
 tgtaatccca gcactttggg agcacaagat gggaggatca cttcagccca agaatttaat 360
 taagaccaac cagcctgggc aaaaaagtga gactccatct ctacaaaaaa tcaaaaaatt 420
 aaccagtcac ggtggtgtgt gcctgtggtc caaactacat gggagactga ggtgggagga 480
 ttgcttgagc ccaggaggtc aagactgcag tgagttatgc tcatgccact gcactccagc 540
 ctcggcaaca gaatgagaca ctgtcttaaa aaaaagamaa gtgaatttat aaacaaaatt 600
 ttaaaaaatc agctcttgta aaaactaaga gtgagaactg actcattatt gcaaagataa 660

cactaaccta ttcataaggg atctgtccca ttatccaaac acctcccacc aggccccacc 720
 tttacaatg ggaatcaaa 739

<210> 115
 <211> 529
 <212> DNA
 <213> Homo sapiens

<400> 115
 aatttcaaaa acaacgaaac cttcttttgc cccctccgca gcagtcgcct ccgggcttta 60
 ttgcaagttt acggttccat acaagtaaat ccgaaaaaaa gtgtgtgtgg ggggggtccac 120
 accactaatt attatggcga ggaagataaa gaagacatgg acagaaggcg gatggctctg 180
 cggcctggct cccgcagacc gaccgccttc ttcttccatt cgagatggct cgtaccgaac 240
 ctcttgcct tcttctggg tctctcgggg gctggaccaa tacatctgcc gatgccctgg 300
 ccgaatggca ggcgacatcg ggtcctggac cccacacgc agctcagtac ccacgaggcc 360
 ccaggccgct ggaagcctgt agctccgagg aggatgaaag cctgcccgcga ggttctcctg 420
 gagtggtag cctctgtcgg aagggggcgc ccacgtcttt ttaatgggcc taacacacca 480
 gtggaataaa tctctaagat tccaaaaaaa aaaaaaaaaa aaaaaaaaaa 529

<210> 116
 <211> 751
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (657)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (658)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (691)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (717)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (726)
 <223> n equals a,t,g, or c

<400> 116
 tggatccccc gggctgcagg aattcggcac gagtttcagg gcaattttat ttcctctgag 60
 agcttgtggt cacctctatg ccagtgatta ccaaactaaa tctctagtct tggcttttct 120
 cttaaactca taaatctatt ccacatttct atcctcgtga tagacttttt tgggatggag 180
 tttctccaac tcaaacctat tttaccacct ttcccttcaa gcttgctcct cttactaatt 240
 tctcagtgtc tgctgttggt gccactattt tctcagagat aaactttgga gttctactag 300
 gtgcctcatt tctctcacct gtcacatcct gtcagtggcc aatgatgtcc attcactgtg 360
 tacagcctct cctcccatta tttttgccat cgtcttattt caagcaattc ttattacttc 420
 cctggacttt tggagtagcc ctctaattgg tttacagtct ccaattggtt ttcctaatac 480
 atcttataaa atactgatga cttttcctaa aaccaatcat gcgaaacctc agcctaaaat 540
 tcttcattgga gtttgattat ctactgaaga aaatgcaaac ttagcgtgac attccagatt 600
 ttcttggtcc ccgcctacct ttctaatttt atctaattct tacctttaat tcttggntta 660
 tacctttctg ataacagtca ctggtttcag ntagaaagct gaaaaggaca ctaacanttt 720
 ggtagnaatt gctaaatgcc ttatatatgg c 751

<210> 117
 <211> 660

<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (17)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (67)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (71)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (159)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (209)
<223> n equals a,t,g, or c

| | | | | | | | |
|------------|-------------|-------------|-------------|-------------|------------|--|-----|
| <400> 117 | | | | | | | |
| ctggagcctg | aaagacnctt | accatthttgt | taggaaatgc | taaatgccta | atatatgtca | | 60 |
| cttaatngca | ngcataggta | agataggtht | aattcccatt | ttaaagggtga | agtaactgag | | 120 |
| gtttcagaga | gttcagggtta | atttgtccaa | gatcatacna | cttgcaagta | gagcaatcaa | | 180 |
| ggttgggtga | ttataaatatc | cacatgctnt | ctgtcacggt | gtgttaattc | tttgtgtaca | | 240 |
| tgtcattttc | ccattgctta | actttgggtta | atcttaaaag | aaggattgct | gaatcaaagt | | 300 |
| atatatccat | ttaaaatgtg | acacacattt | tcaaactgcc | ttctagaaaag | gttataccag | | 360 |
| gctaggtgca | gttgtctcat | gcctgtaatc | ctagcacttt | gggaggctga | ggwrrrcgga | | 420 |
| cagcttgagc | tcaggagtgc | aagaccagcc | tgggcaacat | ggtgaaaccc | tgtctctgta | | 480 |
| aaaaatacaa | aattggccgg | tcgtgggtgg | gcattgcctat | agtcccagag | attgaggtgg | | 540 |
| gaggatcgct | tgagcctggg | agatgaaggt | tgagtggaag | ctgagattgc | accactgcac | | 600 |
| cacagcctgg | tgacagagtg | aggccctgtc | tcaaaaaaaa | aaaaaaaaaa | aaaaactcga | | 660 |

<210> 118
<211> 1488
<212> DNA
<213> Homo sapiens

| | | | | | | | |
|------------|-------------|------------|-------------|-------------|------------|--|------|
| <400> 118 | | | | | | | |
| gagctgcccc | gtccagggtc | atgttcctct | tattttctct | cacgtgtgag | ctggctgcag | | 60 |
| aagttgctgc | agaagttgag | aaatcctcag | atgggtcctgg | tgctgcccag | gaaccacgt | | 120 |
| ggctcacaga | tgtcccagct | gccatggaat | tcattgtctgc | cactgaggtg | gctgtcatag | | 180 |
| gcttcttcca | ggatttagaa | ataccagcag | tgcccatact | ccatagcatg | gtgcaaaaat | | 240 |
| tcccaggcgt | gtcattttggg | atcagcactg | attctgaggt | tctgacacac | tacaacatca | | 300 |
| ctgggaacac | catctgcctc | tttcgcctgg | tagacaatga | acaactgaat | ttagaggacg | | 360 |
| aagacattga | aagcattgat | gccaccaa | tgagccgttt | cattgagatc | aacagcctcc | | 420 |
| acatggtgac | agagtacaac | cctgtggcct | ccccagagta | tgaagagAAC | atgcacagat | | 480 |
| accagaaggc | agccaagctc | ttccaggggg | agattctctt | tattctgggtg | gacagtggta | | 540 |
| tgaaagaaaa | tggaaggtg | atatcatttt | tcaaactaaa | ggagtctcaa | ctgccagctt | | 600 |
| tggaatttta | ccagactcta | gatgacgagt | gggatacact | gcccacagca | gaagtttccg | | 660 |
| tagagcatgt | gcaaaacttt | tgtgatggat | tcctaagtgg | aaaattgttg | aaagaaaatc | | 720 |
| gtgaatcaga | aggaaagact | ccaaagggtg | aactctgact | tctccttgga | actacatatg | | 780 |
| gccaagtatc | tactttatgc | aaagtaaaaa | ggcacaactc | aaatctcaga | gacactaaac | | 840 |
| aacaggatca | ctaggcctgc | caaccacaca | cacacgcacg | tgacacacag | cacgcacgcg | | 900 |
| tgacacacac | cacgcgcaca | cacacacaca | cacacacaga | gcttcatttc | ctgtcttaaa | | 960 |
| atctcgthtt | ctcttcttcc | ttctttttaa | tttcatatcc | tcactcccta | tccaatttcc | | 1020 |
| ttcttatcgt | gcattcatac | tctgtaagcc | catctgtaac | acacctagat | caaggcttta | | 1080 |
| agagactcac | tgtgatgcct | ctatgaaaga | gaggcatthc | tagagaaaga | ttgttccaat | | 1140 |

| | | | | | | |
|-------------|------------|-------------|-------------|------------|------------|------|
| ttgtcatttta | atatcaagtt | tgtatactgc | acatgactta | cacacaacat | agttcctgct | 1200 |
| cttttaaggt | tacctaaggg | ttgaaactct | accttctttc | ataagcacat | gtccgtctct | 1260 |
| gactcaggat | caaaaaccaa | aggatggttt | taaacacctt | tgtgaaattg | tctttttgcc | 1320 |
| agaagttaaa | ggctgtctcc | aagtcctctga | actcagcaga | aatagaccat | gtgaaaactc | 1380 |
| catgcttggt | tagcatctcc | aactccctat | gtaaatacaac | aacctgcata | ataaataaaa | 1440 |
| ggcaatcatg | ttaggaaaaa | aaaaaaaaaa | agggggggccg | ttttaaag | | 1488 |

<210> 119
 <211> 656
 <212> DNA
 <213> Homo sapiens

| | | | | | | |
|------------|------------|------------|------------|-------------|-------------|-----|
| <400> 119 | | | | | | |
| gatggggctg | acgtcaacta | ccagagcaaa | gaagggaaaa | gtcctctgca | catggctgca | 60 |
| atccatggcc | gtttcacacg | ctcccagatc | ctcatccaga | atggcagcga | gattgattgt | 120 |
| gccgacaaat | ttgggaacac | gccactgcat | gtggctgctc | gatatggaca | cgagctgctc | 180 |
| atcagcacc | tcatgaccaa | tggcgcagat | accgcccggc | gtggcatcca | tgacatgttc | 240 |
| cccctgcact | tagctgttct | ctttggattc | tctgactgtt | gtcgtaaagct | tctttcctca | 300 |
| ggtcagttgt | acagcattgt | gtcttcactc | agcaatgagc | atgtgctttc | agctgggttt | 360 |
| gacatcaata | cacctgacaa | ccttggccgt | acctgtcttc | atgctgctgc | ttccggaggg | 420 |
| aatgttgaat | gtcttaattt | gctgttgagc | agtggagctg | acttgaggag | gagggacaaa | 480 |
| tttggcagga | ccccactgca | ctatgcagct | gctaaccgta | gctaccagtg | tgacagtaaca | 540 |
| ttggtgactg | ctggggcagg | tgtcaacgag | gccgactgta | aaggctgctc | tcccctccac | 600 |
| tacgctgccc | cttctgacac | ttacaggaga | gcggaacccc | atacaccttc | cagcca | 656 |

<210> 120
 <211> 1394
 <212> DNA
 <213> Homo sapiens

| | | | | | | |
|-------------|------------|-------------|------------|-------------|-------------|------|
| <400> 120 | | | | | | |
| gttacttaaa | ggtaacatca | cataactaaat | gtcttctata | atcctatatt | tattaatgca | 60 |
| ttacaactct | gtagattggt | agttactagg | ccagtagcta | ggaattggta | taaatttaaat | 120 |
| gcacctttcta | tcctgaataa | ctagcatgga | aaagtgaata | tatgtgtgag | cagatatggc | 180 |
| tataaagacc | tatagctttt | gcacttttat | catatataat | caatcctttc | tagttcagtg | 240 |
| aattgacccc | atccacaggg | tgattcatct | tttgtttaag | gggcaaatga | aacggtatat | 300 |
| tatttctttg | cagtctcttc | tcagtcattc | atcaatgtgg | ccagcttata | tactcccaat | 360 |
| tatgttgttg | atacatctcc | aagccatctg | tcatcagatc | aaaaagcagc | aaacagaggg | 420 |
| tcagtcacag | gatgttctga | cacaccattg | taactttttg | ttagagatga | tcccatttag | 480 |
| aaaaagactg | gtagaaattg | gagtgaaagg | aaccctacag | attagcccag | ttctctctta | 540 |
| ttttcagctt | tacagacaag | aacaatttaa | atctaaagaa | tttagtagat | tccttcagtg | 600 |
| tcacaaagct | gtttcatgaa | agaatcaaga | ttataacctg | gatattctga | ctcctggccc | 660 |
| agtgcctttt | cttactttgt | agctacactt | tgaagtaaga | ttcaaactgt | tatccactca | 720 |
| attgccttat | tcctgaggat | gtagtgaagg | aagaaaaagt | tttctggaat | tccgtaaact | 780 |
| atattttaag | cttatttctt | caaaattatt | ttcatatata | acagatatata | cattggaaga | 840 |
| tataatttgc | atatatgttc | attatcagtg | ttcctaattt | ggtattacat | gtattctatt | 900 |
| tttttctgaa | tgatagcatg | aaaagtgtca | aagtggtttg | tccgctagcg | tctgtctgca | 960 |
| gaactttcag | gatgactatt | aattcctctc | agatgtcatt | tttgagtggg | ccaagcctgc | 1020 |
| tgttttgaac | ccacagcagt | ggagatttgt | attcttattt | acagttgtgt | actataaagt | 1080 |
| gtgtgttaca | taggttttgt | gtaataatta | tttgtaaata | ttatttagat | ttgtatttag | 1140 |
| acatgattta | tatctaatat | agatacaaaag | tctgtgtcta | aatattattt | aaagaagtga | 1200 |
| tttttcatte | tcttggattc | tttccagtg | ggtgcctttt | atatgcctca | catagtctcc | 1260 |
| ttgttctctt | actaatattc | ccaagctcca | tatgccaatt | aaagaagaaa | caaaaataaa | 1320 |
| agtttgtctt | gcttgtgaaa | cattaaaaaa | aggctgtcag | gtttaataar | ctttttaatg | 1380 |
| aawattcrga | catg | | | | | 1394 |

<210> 121
 <211> 1164
 <212> DNA
 <213> Homo sapiens

| | | | | | | |
|-------------|------------|------------|------------|------------|------------|-----|
| <400> 121 | | | | | | |
| tggttggtatc | tcaaataaag | tctgaagatc | acggctcagc | ccagattggt | cccctggcca | 60 |
| actccacagg | tttgaacctg | gcattcttga | caccagctat | gcctcctcca | tttctcagaa | 120 |
| aacctttgat | cttgtgtgtc | tttcttctca | ctgaagggaa | ttgtgggggc | agttcttttg | 180 |
| ccttcttggct | gaacttttgc | ggaaatagcc | cacaattttt | atcagaggtt | agaactgtac | 240 |

| | | | | | | |
|------------|-------------|------------|------------|-------------|-------------|------|
| attatcagag | agactggaca | ctttatcccc | tagcaaagt | ggagaagatt | ttaccagctc | 300 |
| attccactcc | accctggcct | tccccacccc | cccaccccca | gcagcatttc | catggaaatc | 360 |
| cagatggctg | tgtagtgtta | tggctctctt | gtgatagact | ggccttcata | ttggagagct | 420 |
| agggagagcc | cctgggaggg | agagagataa | ggcgtatct | gccttcaatc | agaaccttcg | 480 |
| gtttaaaatc | atctaagagt | ctatacttgt | gtgtacatac | gtatttatatt | ttatttatatt | 540 |
| ttatacaatt | ccattggcat | ggtccttcac | cgaccctatg | atgtgcactt | tttattttcta | 600 |
| tgtgtgccac | acacaatgca | gtattaatgg | caaccaggta | aataattgatt | tatttttttaa | 660 |
| agcttttctt | cagtgttttg | tcaaccattt | caaagtgtct | cccaaaaaag | gatgctgaag | 720 |
| agcaattgct | cccttaagca | acagattcat | atttaccctg | ggttaatata | acaaaaggcc | 780 |
| tgtataattg | tcttttcatt | gttaacaccc | aaaatagcat | ctatctagac | agtatcccca | 840 |
| aagaatttgg | aaaaactgat | ggtgtgagca | gcagccgtta | gtatcagggt | ttccattctt | 900 |
| tggacagtcc | gaggctgtga | cctgttagat | aattagatta | tacttgaact | ggaccagagt | 960 |
| ttgttttttg | aatttatgag | aaaaaccaa | acactaagtt | aagtttgaac | ttgtaaagta | 1020 |
| ttgaaatttg | ttgagtgtcc | tataaattgt | cactactttt | cctgatctgt | ataactgact | 1080 |
| gcaaagtgtt | tgttttttaca | aaagagaaaa | gaaaagattt | ttaataaaga | gaatttgaaa | 1140 |
| gctgaaaaaa | aaaaaaaaaa | aaaa | | | | 1164 |

<210> 122

<211> 2793

<212> DNA

<213> Homo sapiens

<400> 122

| | | | | | | |
|-------------|-------------|------------|-------------|-------------|------------|------|
| tgagaagact | ggagctccga | ggagctgcat | ctgcggcaac | ctgtgtgctg | acgctacgtg | 60 |
| cctcctggct | ccgacgtagc | tgcagctcc | ccagtctcac | tccattcctt | ccccacctgg | 120 |
| cgcgcacctg | ctcaagacca | gggtcctgcc | aagcgctagg | agggcgcgctg | ccagggggcg | 180 |
| tagggaaactg | cggagcgcgc | gcgccatggg | gccgcgcgct | ggggcggggg | tctcctgccg | 240 |
| cgggtggctgc | ggcttttcca | gattgctggc | atgggtgctt | ctgctggccc | tgagtccgca | 300 |
| ggcaccgggt | tcccgggggg | ctgaagcagt | gtggaccgcg | tacctcaacg | tgtcctggcg | 360 |
| ggttccgcac | acgggagtga | accgtacggt | gtgggagctg | agcgaggagg | gcgtgtacgg | 420 |
| ccaggactcg | ccgctggagc | ctgtggctgg | ggctcctggt | ccgcccgcgc | ggcccggggc | 480 |
| gcttaacgcc | tgtaacccgc | acacgaattt | cacggtgccc | acggtttggg | gaagcaccgt | 540 |
| gcaagtctct | tggttggccc | tcatccaacg | cggcgggggc | tgcaccttcg | cagacaagat | 600 |
| ccatctggct | tatgagagag | gggctgctgg | agccgtcatc | tttaacttcc | ccgggacccg | 660 |
| caatgaggtc | atccccatgt | ctcaccgggg | tgcagtagac | attgttgcaa | tcatgatcgg | 720 |
| aatcttgaaa | ggcacaaaaa | ttctgcaatc | tattcaaaga | ggcatacaag | tgacaatggt | 780 |
| catagaagta | gggaaaaaac | atggcccttg | ggtgaatcac | tattcaattt | tttttcgttt | 840 |
| ctgtgtcctt | ttttattatt | acggcgggca | ctgtgggcta | ttttatcttt | tattctgctc | 900 |
| gaaggctacg | gaatgcaaga | gctcaaagca | ggaagcagag | gcaattaaag | gcagatgcta | 960 |
| aaaaagctat | tggagggtt | caactacgca | cactgaaaca | aggagacaag | gaaattggcc | 1020 |
| ctgatggaga | tagttgtgct | gtgtgcattg | aattgtataa | accaaattgat | ttggtacgca | 1080 |
| tcttaacgtg | caacctatatt | ttccataatg | catgtgttga | cccattggctg | ttagaacaca | 1140 |
| ggacttgccc | catgtgcaaa | tgtgacatac | tcaaagcttt | gggaattgag | gtggatgttg | 1200 |
| aagatggatc | agtgtcttta | caagtccctg | tatccaatga | aatatctaat | agtgcctcct | 1260 |
| cccatgaaga | ggataatcgc | agcgagaccg | catcatctgg | atatgcttca | gtacagggaa | 1320 |
| cagatgaacc | gcctctggag | gaacacgtgc | agtcaacaaa | tgaaggtcta | cagctggtaa | 1380 |
| accatgaagc | aaattctgtg | gcagtggatg | ttattctcta | tgttgacaac | ccaacctttg | 1440 |
| aagaagacga | aactcctaata | caagagactg | ctgttctgaga | aattaaatct | taaaatctgt | 1500 |
| gtaaatagaa | aacttgaacc | attagtaata | acagaactgc | caatcagggc | ctagtttcta | 1560 |
| ttaataaatt | ggataaattt | aataaaataa | gagtataact | gaaagtgtct | agatgactaa | 1620 |
| tattaygcta | tagttaaatg | gcttaaaaaa | ttaacctgtt | aacttttttc | cacaaactca | 1680 |
| ttataatatt | tttcataggc | aagtttcttc | tcagttagtga | taacaacatt | tttagacatt | 1740 |
| caaaactgtc | ttcaagaagt | cacgtttttt | atttataaca | attttcttat | aaaaacattg | 1800 |
| tgtcttttaa | attgtggagt | gctgtaatca | ctttatttta | tgatagtatc | ttaatgaaaa | 1860 |
| atactacttc | tttagcttgg | gctacatgtg | tcagggtttt | tctccagggtg | cttatattga | 1920 |
| tctggaattg | taatgtaaaa | agcaatgcaa | acttaggcga | gtacttcttg | aaatgtctat | 1980 |
| ttaagctgct | tttagttaat | agaaaagatt | aaagcaaaat | attcattttt | actttttctt | 2040 |
| attttttaaa | ttaggctgaa | tgtacttcat | gtgatttgtc | aaccatagtt | tatcagagat | 2100 |
| tatggactta | attgatgtgt | atattagtga | catcaacttg | acacaagatt | agacaaaaaa | 2160 |
| ttccttacaa | aaatactgtg | taactatttc | tcaaacttgt | gggatttttc | aaaagctcag | 2220 |
| tatatgaatc | atcatactgt | ttgaaattgc | taatgacaga | gtaagtaaca | ctaataattg | 2280 |
| tcattgatct | tcgttcatga | attagtctac | agaaaaaaaa | tgttctgtaa | aattagtctg | 2340 |
| ttgaaaatgt | tttccaaaca | atgttacttt | gaaaattgag | tttatgtttg | acctaaatgg | 2400 |
| gctaaaatta | cattagataa | actaaaatc | tgtccgtgta | actataaatt | ttgtgaatgc | 2460 |
| attttctctg | tgtttgaaaa | agaagggggg | gagaattcca | ggtgccttaa | tataaagttt | 2520 |
| gaagcttcat | ccaccaaaagt | taaatagagc | tatttataaa | tgcactttat | ttgtactctg | 2580 |

| | | | | | | |
|------------|------------|------------|------------|------------|------------|------|
| tgtggctttt | gttttagaat | tttgttcaaa | ttatagcaga | atttaggcaa | aaataaaaca | 2640 |
| gacatgtatt | tttgtttgct | gaatggatga | aaccattgca | ttcttgtaca | ctgatttgaa | 2700 |
| atgctgtaaa | tatgtcccaa | tttgtattga | ttctctttaa | atataaaatg | taaataaaat | 2760 |
| attccaataa | aaaaaaaaaa | aaagggcggc | cgc | | | 2793 |

<210> 123
 <211> 511
 <212> DNA
 <213> Homo sapiens

| | | | | | | |
|-------------|------------|------------|------------|------------|------------|-----|
| <400> 123 | | | | | | |
| tgggaattccc | aaggtgctgg | aggttgaaag | gcattgagaa | tctaaaacgc | tttgagaca | 60 |
| gcaagaccct | ctgtgtaagt | taagaatgct | cactcagtc | cagcaggtac | tcagagggat | 120 |
| ccttttattt | ctccagaaca | ttctgcaggt | gagctgggga | agccactgg | ccctggcctc | 180 |
| acccccgagc | ccgagccttc | agcctgggaa | tggctctggc | tcttccttgc | tggctctcca | 240 |
| gcctggcctc | gcaggaccct | gggcgggacc | ccaggaaccc | tcaccgccta | tgtgcttccc | 300 |
| caagaagcgc | tccctgyggc | ctaatttgag | aaaacaatgg | gcctcaatcc | atattaatga | 360 |
| ccctagaggg | accctttgtc | ctcggtgcac | aggctgtaat | cagcgkrc | ccgggrgctc | 420 |
| tggcctaatt | tggagggaca | ggttttatca | tcacccttga | ttcggtgac | ccaatctgac | 480 |
| aggcccacga | ccccctgtat | gcggggtcca | c | | | 511 |

<210> 124
 <211> 581
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (496)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (580)
 <223> n equals a,t,g, or c

| | | | | | | |
|------------|------------|-------------|------------|------------|------------|-----|
| <400> 124 | | | | | | |
| ccggacgcgt | ggggtctact | aaaaatagaa | aaattagcca | ggcgtggtgg | caggcccctg | 60 |
| taatgccagc | tactcaggag | gctgaggcag | gagaattggt | tgtatccggg | aggcggagtt | 120 |
| tgcagtgcgc | cgagatcggt | ccactgcact | ccagcctagg | caacaaacca | agactccatc | 180 |
| tcaaaaaata | aaaataaaaa | aagcagggtga | tgggatgaca | tggagttttt | gttttgcttt | 240 |
| gttttgcttt | gttttgcttt | ttgctgcttc | cctgataggc | tatatactgc | tcccttcagc | 300 |
| ctctccccga | aaccacaggc | gccccaaaca | tgaggccagg | gttggaaacc | ctggccagct | 360 |
| agatgatgag | ctgaagggga | ggcaaccttt | agccagcaga | cttgagacat | ctcagtgtac | 420 |
| tcagggtctg | ctggctagca | ggcccgatgg | ggtctccaaa | gcccttctgt | atccttaatg | 480 |
| gtccttaaac | cctggntgaa | gatcccccca | gttggtgtta | cttaagccag | aaggctgggc | 540 |
| aatctctata | tcctttctcc | atcgatcatc | ctatgattgn | t | | 581 |

<210> 125
 <211> 1166
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (1163)
 <223> n equals a,t,g, or c

| | | | | | | |
|------------|------------|------------|------------|------------|------------|-----|
| <400> 125 | | | | | | |
| aatcaccagt | tccgtgtcca | ctatccgaca | gtatccagtt | tcagctcagg | ctccaaactc | 60 |
| tgccatcaca | gctcagactg | gtgttgggg | agcgtctacc | gtccacctaa | accccatgca | 120 |
| gttgatgaca | gtggatgcat | cgcatgctcg | acatattcaa | gggatccagc | cagcaccat | 180 |
| cagtaccag | ggtatccagc | cggcccccat | tgggacccca | gggatacagc | ctgcaccact | 240 |
| tggcacacag | ggaattcamt | cagcaacccc | aatcaacaca | caagggcttc | agctgcacct | 300 |
| atgggtactc | agcagctcag | cctgaaggaa | agacttcagc | agtgggtgtg | gcagatggag | 360 |
| ccacaattgt | ggccaaccct | attagcaatc | cattcagtg | tgctccagca | gaacaactgt | 420 |

| | | | | | | |
|-------------|------------|------------|------------|-------------|------------|------|
| ggtgcagacc | cacagccaga | gtgctagcac | caacgctccc | gcccagggst | catcgccamg | 480 |
| gſcaagcata | mtccggaaga | aacctgccac | agatggaatg | gcagttcgga | aaaccctcat | 540 |
| tcctcctcag | cctcctgatg | ttgctagtcc | tcgagtggaa | agctctatgc | ggagtacgtc | 600 |
| tgggtcacct | aggcctgcag | gtgccaaacc | caagtctgaa | atccacgtgt | ctatggccac | 660 |
| tccggctcact | gtgtccatgg | agactgtatc | caatcaaaat | aatgatcagc | ctaccattgc | 720 |
| cgtccctcca | actgcccagc | agccccacc | gaccattcca | actatgattg | cagcagccag | 780 |
| tcccccgctca | caaccagccg | ttgccctttc | aaccattcct | ggagcgggtcc | ccatcactcc | 840 |
| acccatcacc | accattgcag | ctgcaccacc | tccatcagtc | actgtgggtg | gcagtctttc | 900 |
| ctccgtcttg | ggccctcccc | ttcctgaaat | taaagtgaaa | gaagaagtag | aaccaatgga | 960 |
| tatcatgagg | ccagtttctg | cagttcctcc | actggctacc | aacactgtgt | ctccatctct | 1020 |
| tgcattgctg | gcaaacaact | tgtccatgcc | tacaagtgac | ctaccacctg | gtgcctcccc | 1080 |
| aaggaaaaag | cctcgaaagc | aacagcatgt | gatctcaaca | gaagaagggt | acatgatgga | 1140 |
| gacaaacagc | actgattaat | ganaaa | | | | 1166 |

<210> 126

<211> 692

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (1)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (8)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (12)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (32)

<223> n equals a,t,g, or c

<400> 126

| | | | | | | |
|-------------|------------|------------|------------|------------|-------------|-----|
| ntttgcengg | tnctgtttt | aatcacttga | tnataaactt | ctggaaaaag | atcattatatt | 60 |
| tcactctgaa | atttccatac | agcaagtatt | caataagtgt | ttggcagatg | gatgaatggg | 120 |
| cagatattat | aggttcttac | catgttgatt | atgaagaagt | acaaagtatt | cagaataaaa | 180 |
| acactaagca | cagtaataaa | ccaaggggtg | gccagtaaat | ttaccagta | aattataact | 240 |
| ttcaaaaact | gacggttctt | aaataaaact | taatctctgc | actatttccg | ggaatwtcac | 300 |
| acatggttat | tacagttgat | tatttcaggg | aggcagttcc | tctgctaata | atagttgtga | 360 |
| actggctgga | cagaggcctg | gaagacacca | gactttctct | tctgaattaa | ctccacagtg | 420 |
| ttttgttggt | gctcttgccc | tgaccrawrt | tactcttmta | gcctagagta | gtggttctca | 480 |
| gctctgactg | agcatccaaa | tcccccatgg | agatttttca | aggcataatt | atctaaatcc | 540 |
| cactgcccag | attatgattc | tgtcggctga | gtaggggtct | atgtgctcac | atgttctaaa | 600 |
| aactctagag | acatttctga | tgcatagcca | ggttcaagaa | taactatttc | aaaagtcacc | 660 |
| cacagggttaa | aaaaaaaaaa | aaaaaaactc | ga | | | 692 |

<210> 127

<211> 675

<212> DNA

<213> Homo sapiens

<400> 127

| | | | | | | |
|------------|------------|-------------|------------|------------|------------|-----|
| atctctgacc | tcgtggggcg | tgtgggtctcc | ggatggctgg | gagatgcagt | cccagggcct | 60 |
| gtgacacgac | tcctgatgct | ctggaccacc | ttgactgggg | tgctactagc | cctgttccct | 120 |
| gtagctcagg | ctcccacagc | cctgggtggct | ctggctgtgg | cctacggctt | cacatcaggg | 180 |
| gctctggccc | cactggcctt | ctccgttctg | cctgaactaa | tagggactag | aaggatttac | 240 |
| tgtggcctgg | gactgttgca | gatgatagag | agcatcgggg | ggctgctggg | gcctcctctc | 300 |
| tcaggctacc | tccgggatgt | gacaggcaac | tacacggctt | cttttgtggg | ggctggggcc | 360 |
| ttccttcttt | cagggagtgg | cattctcctc | accctgcccc | acttcttctg | cttctcaact | 420 |

| | | | | | | |
|------------|------------|------------|------------|------------|------------|-----|
| actacctccg | ggccccagga | ccttgtaaca | gaagcactag | atactaaagt | tcccctaccc | 480 |
| aaggaggggc | tggaagagga | ctgaactcca | cagagtcagg | cccagaaagc | caaagcttga | 540 |
| cagctccagg | tcttctcttg | ccacgtcttg | gtctccacag | aaccacagtg | ccttaagatt | 600 |
| cttgatctgc | ctccccctag | agcaggcctg | gggctcctgc | aatgtgtgtg | ccaacccttt | 660 |
| gtattttggt | gagga | | | | | 675 |

<210> 128
 <211> 3669
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (199)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (2797)
 <223> n equals a,t,g, or c

| | | | | | | |
|-------------|-------------|-------------|-------------|-------------|-------------|------|
| <400> 128 | | | | | | |
| tcaaaaatag | tgatagcttt | gataatcagc | tcctagacct | agactatccg | tctaagaggg | 60 |
| aagctacagg | gcaaggctag | gtcacccctga | tctcctagca | gcttatcaaa | agaattatat | 120 |
| gggcaagttg | gcaaggctccc | tgctgtgaac | gaaatcatct | gtccatctca | agatgaagat | 180 |
| attccaacat | gcacctatna | agaaaaccac | tgctaagatt | tgagttctgt | gaacctgcat | 240 |
| ttgttgttgg | taattgcctc | cagatagctt | ctgacagtca | tcagtatgat | cgaattttatt | 300 |
| gtggagctgg | agtacagaaa | gaccatgaaa | actacatgaa | aatattacta | aaagttggag | 360 |
| gcatattagt | catgcctata | gaggatcagt | taacacagat | tatgcgaact | ggacagaaca | 420 |
| cttgggaaag | taaaaatata | ccttgctgtt | catttgctcc | acttgtgcaa | ccaagtaaga | 480 |
| atgataatgg | caaaccagat | tctgtgggac | tcctctcctg | tgctgtcagg | aatctacagg | 540 |
| acttggctcg | tattttacatt | cgacgcacac | ttagaaattt | cataaatgat | gagatgcagg | 600 |
| ccaaggggat | tcctcaaagg | gctccaccca | aaaggaaaag | aaagagagtt | aaacagagaa | 660 |
| ttaacactta | cgtattttgtg | ggtaatcagc | ttattcctca | gcctctagac | agtgaagagg | 720 |
| atgaaaaaat | ggaagaggat | awcaaagaag | aggaggaaaa | agatcacaat | gaagcaatga | 780 |
| agccagagga | gccacctcaa | aattttactga | gagaaaaaat | catgaagctg | cccctccctg | 840 |
| aatcttttaa | agcttacttg | acatatttta | gagacaaata | acttagatca | agaagaaaaa | 900 |
| tgccctactga | taattccttt | agtcttgaaa | atgtagcatt | tgtaggaggt | taaaagagag | 960 |
| aattatttct | ttcatcagag | caaatttatag | tggaaaaaaa | aatcacttgt | ttctgtcagt | 1020 |
| aacacaaatg | atgtatttcag | tgaataaaaag | aatccctttt | ataaaatcta | tttttcttta | 1080 |
| aatcttggaa | aaatgttgtt | ttagctcaga | gtgatttcaa | agtggaatgc | aacagtagtc | 1140 |
| aagactttgt | tactataaat | ccttttctga | ttccttacag | atgtgtagtg | atgaggttta | 1200 |
| gattttaatt | tatatatggg | ttaaataaatt | gttaagctta | tataacctga | tctgaattgc | 1260 |
| agttgtttgc | atttcctcta | tgaaaacttc | atattatctaa | taagggaagtc | aaatgctttg | 1320 |
| tagactattt | accttacttt | tggttgcaatc | actgttgttg | gggtgtgtga | tatatattcc | 1380 |
| gggcaatata | tgagtgcaat | aacaatacaa | gatattgaat | aatttagctt | taaaaaatcc | 1440 |
| cacaaatttt | atgaaaatttt | acagccctgc | tacttttgct | tttgaatctc | ttgccaaaag | 1500 |
| acatgggtta | aatatctgcc | tctctcatag | agatttttaag | agcacagcaa | gtgaattatt | 1560 |
| aaaacaaagt | ctatacttaa | tacaactctt | tatatggacc | ctttacattt | tcagtattta | 1620 |
| aaaaaaataa | ctctatagaa | ttttaaaagt | atattttagaa | ttgttttttc | tgtagttcac | 1680 |
| tgtataaagt | atgttggttt | ttaaaaaaag | caaaaccatt | gttatgtgtg | actcttgata | 1740 |
| ggacacagaa | cgagtgaatg | agcatgagtg | aggccacttt | cttggatggc | tgtaagtagc | 1800 |
| agggccaggg | tagacttggt | cagcggatgc | acttttagcag | atggaaacttc | tagtttatct | 1860 |
| gaatatttat | cttttgacaag | gtagggtctga | gcctacattt | gcttttgatc | tatctagtat | 1920 |
| aagaaatatt | cacagaaatt | gtatgtagat | accctttgtt | ttgaaaatgc | tgttcagaat | 1980 |
| catagtgtaa | tctttgggac | ctatgccatg | ttcatttcac | tccttcccat | attttttgtg | 2040 |
| tttcttttgg | taaaactata | atggttttca | ttttttactt | aatatcacac | agttaaactg | 2100 |
| tccatatttg | agcttttatt | tagcttatca | gtgataaaaa | acaggtagta | actgccattg | 2160 |
| tttgttttgt | ttcctaataa | ggcctgaaaa | cagccattcc | ttgttaagaa | agtgtacaat | 2220 |
| gtaacataat | tgctagagtt | acatggatta | tatatattct | aaagggaata | atgttagagt | 2280 |
| atcatggact | accaccagca | ttattattac | agtagttact | cagatttggt | taagggaagg | 2340 |
| caagcaatgt | atagtgaag | gattattatc | tctctgctaa | gattcagata | ttgtttcaga | 2400 |
| aatctcagct | ccagtaattc | cacaacatct | aaaaacaaat | gtttgtgatc | atgtgtaagc | 2460 |
| atgaaattgt | tccaagtaag | tgaggatatt | ttagttatgt | gaaagacagt | ttcatggaag | 2520 |
| gtatttgttt | tataccagtg | gctgggatgg | tggaattggg | gttatttcta | caattattct | 2580 |
| tagacgatta | ctaaactgtt | aagaaatgcc | ccatatcatt | tttgtatcta | ggaaagaaaa | 2640 |

| | | | | | | |
|------------|-------------|-------------|------------|-------------|-------------|------|
| aaatcagttt | catactgttg | tcactctgtca | gaaatgctca | ttttattttg | aattaaatgt | 2700 |
| ggcttttgaa | gtacctagtt | accttgaatt | cctggtgacc | acatgttttt | atctggaaaa | 2760 |
| cctggagaaa | gttatctgtc | ccatctcccc | tgcttgnttt | tttttttttt | tttttttggt | 2820 |
| tggagctgct | gttttagatga | tgcttttact | atgcaggaga | gagtttttgt | taaggatata | 2880 |
| tttgaagatt | ggcttttcca | tattgtcctt | cattccttga | ccgtggcaaa | gtgtacagta | 2940 |
| gatttttcag | atcattgcat | atttcttgtc | attgaaatgt | atcttttatg | tttttaaattg | 3000 |
| cattcatttt | acacttgtga | gtttatcatt | gactttaaga | ggtagaaatg | aaaaatgaaa | 3060 |
| attaaagcta | aagccttttt | atctattaat | gcagatatat | tagaataaga | atattttggg | 3120 |
| tttgtgttta | ttttttaatg | aatttatgtt | tacttgatat | ggaaaattac | gctttatagg | 3180 |
| tggaaaagta | gcaataaag | attaagtaaa | agtaagtga | aatgatgggg | aatatagtat | 3240 |
| tggaaattta | tagctagtta | aaacaataag | tatcatctaa | tttgggtgtt | tattttgcag | 3300 |
| atgagaaaac | agacctagaa | ccgtggcatg | ttttgcctga | aacatrcagt | gagttagaga | 3360 |
| cagggcctaa | gatagcttct | agcatcagat | caatcccaag | aatccatcag | caacctcaga | 3420 |
| ccaacccaag | aagataattt | aaatctatac | tgcttattgg | tcaatatatt | tggttctagt | 3480 |
| attaataaag | aaaaatgtta | ttaaaatagc | atacatagta | gtaaaaataaa | atacaaaaag | 3540 |
| tgtgttgatt | tatagctgtt | tgagatgata | aaagtgaagc | aaagcctgtt | aaatcattgg | 3600 |
| aagacttgga | aaattatttt | aaataaacia | ttacatgtaa | ttaaaaaaa | aaaaaaaaaa | 3660 |
| aatactgcg | | | | | | 3669 |

<210> 129

<211> 667

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (571)

<223> n equals a,t,g, or c

<400> 129

| | | | | | | |
|-------------|------------|------------|-------------|-------------|-------------|-----|
| gatactctta | ccttggcctc | ccagaatgct | gggattacag | gtaatgagcc | actgcacccg | 60 |
| gcttgtagca | ttttttaaaa | agttccttca | tacaggccca | ccactcccag | cctcctttat | 120 |
| ccttttgacc | acaagattct | ctaggcacat | cttatatatt | tccggcccca | gtcctagaat | 180 |
| cagccacttc | tccaaggagc | cctgattctt | tttattagag | aatgggtatta | gaaaccaagt | 240 |
| tctaggcatt | gggtgtgctt | gctactggga | tggtgtggct | tgtaggacct | ttcagctgac | 300 |
| tgagcaaggg | atgtacatgt | atgtatacta | aactaagttt | ttctgtatgc | agtcattctgt | 360 |
| atctatatata | agctaaacat | gagttgatgt | ttccaattct | atccattacc | actctatcca | 420 |
| ttctagcctt | cttcccttgg | ttatctgtca | cctctcactt | ctacagacag | aaaactggct | 480 |
| ttcatcattc | accatctttt | tacttaattg | ttcaaactctg | ggatacatat | gcagatatag | 540 |
| tggtttcaga | atacgtattc | ccatggagaa | naaccttatc | aagtagagaa | cagtgtctaa | 600 |
| gtgtagttcc | tggtgccttt | agtcttatag | acttcatttc | caaagtttct | tagcaccccc | 660 |
| cttcccc | | | | | | 667 |

<210> 130

<211> 561

<212> DNA

<213> Homo sapiens

<400> 130

| | | | | | | |
|------------|-------------|------------|------------|------------|------------|-----|
| ggggcttgta | aatgtgtgtg | agtttctgag | tgtaggtgcc | gaataaatgt | ttattgatga | 60 |
| tgccaccta | tgcaatctgc | atggtgcttg | tatttctatt | gcttggtgat | ttgcacatca | 120 |
| taaacacaaa | cacacacaca | cacacacaca | cacacacaca | cacaggcttg | cttccagagc | 180 |
| catacatgct | ctatttttcag | tttctgagtg | tcctaagagg | ttatatcctg | tctagatgga | 240 |
| cggaccgaga | gtacatttgg | atttctacca | agatatattc | tcctaattca | ccagaacccc | 300 |
| ccgcttcctg | cccattcccc | acacagagca | tctcacgcca | tgtagtgtag | ggaagcacat | 360 |
| tectcaaaag | tcagctgccc | acctctgagc | aggtgcaaat | ccacccactg | catcctccca | 420 |
| tccacctttc | tcccctctga | cttctgctct | cctcctaaat | gggtctcttt | ccccctgcct | 480 |
| cctcctcctt | cgtttccctt | ctccagagag | gcagaggtta | gggtgtgctg | accagsattc | 540 |
| accaagtgca | gacatcaaaa | c | | | | 561 |

<210> 131

<211> 702

<212> DNA

<213> Homo sapiens

<220>

<221> SITE
 <222> (693)
 <223> n equals a,t,g, or c

<400> 131
 ggcggagctt gcagtgaacc tagatagagc cactgcactc cagcctgggc cacagagga 60
 gactctgtct caaaaaaaaaa gaaaaaaaaa agaaaaagag aaatctatga catcacttgc 120
 caggctccca tgttcttacc tctgcctgcc ttgccagctc tcctcctgct gtgccttctc 180
 tcagcccatc tctgcacttc ttcccagtc ttcaacacct gtgcttctct ctgccccag 240
 gccttccagc caggggggtcc caggcaccag aagtgaattc ccctcaacc ccttctgtct 300
 gccctccttc ccacgtgaat ccttccttga ttcccttcat ctggtcagct cccattagta 360
 tgcctctctt gcagcctgcc ctttctcttt tcagtgcgtg atcacaactg tattaggcaa 420
 tcacctgtct aatgtctgcc ttcttaatta gaacttcaaa ttcacgtggg cataacatcg 480
 gtctgcctta ttcttctgtg tatcctggat gtcgaacata acacytggca cctgggtggc 540
 aatgattaaa tatttctgtg aagaatgggc aaaataaaaag agtaaaaaaa aatgagtga 600
 agatacagtg aagtgatgtg gcaatattgc taacttttaa aaawttgtca aagagatact 660
 gagtctcagg aagaggaaga tagaaattat gcntggaatg ct 702

<210> 132
 <211> 483
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (416)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (422)
 <223> n equals a,t,g, or c

<400> 132
 gctcgtgccg cttttttcct gccatcggtc agaaaaaaca tgtcgaagat ggatggcatt 60
 agattatgca ggaatttcta ttggaatact gggctgctat gtctcaggag tattttacgc 120
 attttattgt aataactact ggcgtcaggt gtacttgatc acagtgcttg ctatgatcct 180
 ggcagtgttc tttgctcaga ttcatcccaa ttacctcacg cagcaatggc aaaggctccg 240
 ttctatcatc ttttgttctg tttcgggata tggagtgatt cctactcttc actgggtttg 300
 gctcaatgga ggaattgggtg ctctatttgt acaggacttt gcaccccggt taattgtgat 360
 tnatatgatt gctcttcttg ctttcttatt ctacatttcc aaagtcccag agcggnaactt 420
 tncagaatca cttccacggt gaatcatasa agggattgta ccactcgtca cgtgggtggg 480
 aaa 483

<210> 133
 <211> 748
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (6)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (15)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (37)
 <223> n equals a,t,g, or c

<220>
 <221> SITE

<222> (62)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (65)
 <223> n equals a,t,g, or c

<400> 133
 atttttngggg aaccnagatt cttaggggaca atgcccnaacc tgggaatttgg aagcccaccc 60
 cnatncttcc aggcaggccc agaattaccg gaaaacaatt ctggacaact aactacctcg 120
 gattcaagcc caccaaataat ggcatatcct tgcagtagtg atgttatatt ggtggcatca 180
 gtcaacagtg tatgtcatgc agtacagaca tagcaagcct tgtcctgact atgtttcaca 240
 tttgtgaatt agaatcagga acgaagattc aggggaatgtc tgtcacatct tatggcatcc 300
 cacctggaca gaatatccga tttgaagatt gtgattgact tccgtaaaac tgtacaactc 360
 tccatttggc agctgctaca taataggtgc ttaatgtttg tgggtgtgaat gaaataactg 420
 aatttgaata gaagtttaca tccaaaagtc ataataagac aaataatgaa aaactccaaa 480
 gtcactgatt ataaagaata tgcaatccat ttgggattta ttgcatttaa agaaaacaga 540
 ttaaaacagt gcttacgtga agtaccaaaa cctaaaataa accaagcaga gtagctgact 600
 tgtaagaaaa ctgctctgcc tgggtgaactt cagcatagaa gagtgggctc caccttagat 660
 tttccaccag caagaggaca acagtctatc actcttaaac aataaacagg gtaagactga 720
 aaaaaaaaaa aaaaaaaaaa aaactcga 748

<210> 134
 <211> 652
 <212> DNA
 <213> Homo sapiens

<400> 134
 gcccgcacct ggggctctcc gctcgttagc gcgcccaggc cgcctcctcg gcccgagagg 60
 gaccgcgccg cggggcctgg ctggctcagg gctacctcct tccgcctagg accccccctt 120
 cggtgactcc cgattccctg tcctaggctg cggtgccccg ggaggcgggt cgccagagta 180
 gcagacagag ctctttaatg ggtgtcttct agggcggggt ctgtttgtgc atcatttggg 240
 tccccacaca ctctctatga ggtggcgaaa gccattatgc ctatgggtgc tgcctcacaca 300
 gggggaaact gaggcccagg caggacagcc ccttgccctg ggtgggggct gggttgtcct 360
 taggcctgtg acttsacctm tacagcacc cctgtggac cctctccctg ccmccgccag 420
 gccagagtc tgcagccagg cccagaccyt ggccgtgtccg tccgggggatg ctggacagta 480
 ctctctccctc cagccctcat aagtcatkgt cattcggats tgcatttccc cagccctctt 540
 ccttctaast ggggggcact gtggcccaact gtgccccttt ctcttcccat tcttcccccc 600
 tacaccatt ccagacatcc cagagttaac aaaacccaaa aaaaaaaaaa aa 652

<210> 135
 <211> 3006
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (2700)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (2711)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (2808)
 <223> n equals a,t,g, or c

<400> 135
 tttttttttt tttttttttt tttttwttkt tcaagcagaa aacaagctgc ttttattaca 60
 gtatgatgtc atgactcatt tgtaacagat ccagcctcag ggacagccct gtaaggcagc 120
 aagtggggct ggctccaaat gggatatgag ctccagaatct ttggtaaggc agaactgaac 180
 tgggctgaga ggtggtctta aggcctgggc aggcctctatt ctctctggac tggctgcagc 240

| | | | | | | |
|------------|-------------|-------------|-------------|-------------|-------------|------|
| ctgcagtcta | ggagaggccc | agtacagcct | ggagctcctg | agccttgctca | acaggcagtg | 300 |
| agcccagagc | tgcttgaaag | ctgtcgggtgt | gctgtttggc | caggaacgtc | aggagcagca | 360 |
| acagtgcggc | cttggtgtct | ggtgggatct | tggtgtcagc | cagaatgagg | ctgcagatac | 420 |
| gcagaagctc | gggagccaca | tctataacct | ggtcagggct | gctctgggtac | aggaagctga | 480 |
| agaggcgccc | aatggtgacc | cactcctcca | agtccctcct | cagtggcagg | gcatgcagta | 540 |
| gggcagccag | cacctggggc | tctggtttcc | tgggtgggact | ggccatcaac | aggcgggcaa | 600 |
| gtgccccaca | gatgttgtca | cggacacgat | catgtcgctc | ccgcgccagg | aggggaaaaa | 660 |
| ggagccccag | cagcttgggg | aagtgttcct | gggcaggggtg | gccccatgc | tctgccagca | 720 |
| cgcccatccc | gaagatggca | ttgcttcgca | cctcggggct | tgcctcttgg | gcggtgctca | 780 |
| acagcacagg | gagcagccga | gacacaaact | gggctgaggc | agcaccagg | ccctgaatag | 840 |
| tctctgccaa | ggtcccaact | gcaaaggact | tctctgccac | tgtgcagccc | tgttttgtct | 900 |
| tgacaccaa | taatggcagg | aaaccggcaa | agaatggggc | aaaggagtct | ccccagccg | 960 |
| cggctgccag | ggcagggatg | gcctctccag | cgtgctccag | caacatggcg | tcgtattcag | 1020 |
| cctgatcatc | atcttctctc | tcctcctcct | cgtcagtatc | ctgacaggct | gtcttctctc | 1080 |
| gcagcacagc | cttgagcacg | ccacagagct | cagcagggcg | cccagggggc | ttcagtgtga | 1140 |
| gggtcccaca | gctgcggagc | acccctgtca | gggcctccag | cacggccatc | accacctggc | 1200 |
| gttcccgcct | cctgttcaact | gctgcagtg | aggatggcac | gactcgggcc | agggcagcct | 1260 |
| gcaaagcagc | agtgttgggt | tccgaggggc | agctttgaca | ggccttgtgc | agtgcacagc | 1320 |
| aaaactgacc | cagagcctca | tgggctgcct | tccgcacatt | caggtgaggg | cactccagca | 1380 |
| gtttaaatac | ttcttcaaag | acactttcca | tgtatggaag | gaaggccaca | ctgggtgttca | 1440 |
| cagagatctc | ccccacggca | gcacaggtgt | cttcttcttc | atcgaagaag | gcattctcca | 1500 |
| cgctgtaccc | tgagatctyt | gagtcacctc | cttcttccac | atcctcatcc | atgagctcct | 1560 |
| cctcttcttc | cccatactc | tcctcgtcaa | acagaaggaa | ggagctgctc | ccgtcatact | 1620 |
| gaggcacaat | gccctcggtg | gaacgcagtg | acagcagcat | gagcgtgggtg | atctgttcca | 1680 |
| agtggggcgc | caggccctca | cccatcagac | ccgataaggc | tgcaaatagg | ctgtacgtgc | 1740 |
| agcgccgcaa | gtcagcgtcg | tctacctgg | cgcagaggcc | cagaccagc | tggcagcatt | 1800 |
| cctcagccag | cggcctcatg | ggctccccc | ctgctcgtgc | cagcaccccc | agtgtctcca | 1860 |
| ggctctggat | ctgcacaggc | tgaaggctcct | cacggcctgt | taacaggaat | tccgcaggt | 1920 |
| gctccatgat | ggcagggaa | tagggcagca | gcgagrcctg | ggcagccgta | gcaatggctc | 1980 |
| ccaggcgct | cacagccagc | tccttggccc | gggactgct | ggggttcctc | agaagctgca | 2040 |
| gcatgcattc | cataagctcc | ggaaggtagg | gctgcacctt | gggcccctagg | ttctccacaa | 2100 |
| aattctccag | ggcatagcag | gccttggcta | ggtggtgtgt | gtgtccaaga | ggcaccgact | 2160 |
| tcaagtaggc | gaggagcagt | ggcattacct | cccttgaata | gctgctgata | tggggctgta | 2220 |
| ggttttctga | gaactggccc | agggcaaaca | gcgcagcatt | gcgtacaact | tgcgaggggt | 2280 |
| cctccaggcc | cttgccacaca | atctgcagca | gtgggggagc | cagtctctgc | ctgatgtggt | 2340 |
| cgccagctcc | gtcagacagc | acggccagca | ccaggagtca | gctttgcgct | ggtaggggt | 2400 |
| cctctccgca | aagcctcttc | caacatgggc | atcagctggg | gacagagctt | ctcggggggc | 2460 |
| aggtgtagtg | ccagcatgtc | cacaacttgt | acagcgaaat | gcttgggagt | ctccccatc | 2520 |
| agctcaatct | ccaactcttc | ctcttctgaa | tcctggctcct | cgggatccaa | ctggcctggt | 2580 |
| gggggctcag | cagccacaat | ggggaaaagg | gtgtgcagca | aggggtgscag | gagacgattc | 2640 |
| ttcagtaagg | ccttgcctctt | gactttacca | agaaagttag | gcagcagaga | ataccgtatn | 2700 |
| gtatgcatt | nccagggcac | atttctagct | acctcaggc | agaatgtgag | gacttcagag | 2760 |
| aggtaggggt | gatgaccggc | acctctgact | ccaacagttc | atccaaanct | caaggctcac | 2820 |
| agcctttgcc | tcatctatgg | gatcagagtc | tgcatggcca | tgatcagctt | gggcaccaac | 2880 |
| atccgagcga | gaggcacatc | ttcagtgctg | aggtagggag | ccatgggtgt | cagagtgcgc | 2940 |
| agggagtaga | agagcagccc | aggagagccc | acctcaccaa | gagtctcatt | cagaagccgc | 3000 |
| ctgtgc | | | | | | 3006 |

<210> 136

<211> 720

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (657)

<223> n equals a,t,g, or c

<400> 136

| | | | | | | |
|-------------|------------|------------|------------|------------|------------|-----|
| aagcctgggc | ttttgacctg | tccttggagg | cggtgcggcg | gacttttatc | ctctccttgg | 60 |
| gggtccgtggc | gttctgggag | ctgctgacag | cgcctctgga | gcaggtggca | gatgacagcc | 120 |
| tttatgagtt | cctggatttt | gtggatgcca | ctgaccgata | cagaagcctg | tgggtctgga | 180 |
| ggttgtctgg | catgtcggca | ggcgtgtgtg | gcatcacagc | cttgggtggg | cagctggact | 240 |
| gcttctgat | gaccagtggc | ccccgaggtg | tggtccactt | ctatgggtac | tcgggtgtca | 300 |
| gcaccctggc | cttactgggt | agcattgcct | ttccatttcc | catctgtcag | cagtgggagc | 360 |
| ccagctacaa | aagggtcaaa | gcactgtcca | ttgtgggggg | tgacccccc | ctcattctcc | 420 |

| | | | | | | |
|------------|------------|------------|------------|------------|------------|-----|
| tcgcctccac | cactgttttg | gtaggagcca | tcgtcagtag | tgtccagaac | tttctgttct | 480 |
| ggcacatgaa | ggaccatggg | agcggcgagc | tggtcatggg | tttctcgggc | gccctcagct | 540 |
| tgctggggga | aattctgctt | catccgttca | aagctacatt | gcttaggaaa | ctgtccagga | 600 |
| cgggcctsgt | ggggctgggg | ctgagctgcc | tcgctgggca | gctgctgtac | tactctngcc | 660 |
| tgtgagctgg | tggtccgtct | ccccattaag | atctgagtag | cattagcaac | agagcttttt | 720 |

<210> 137
 <211> 463
 <212> DNA
 <213> Homo sapiens

| | | | | | | |
|------------|------------|------------|------------|-------------|------------|-----|
| <400> 137 | | | | | | |
| agggacgtgc | tgggatgtgc | tggccaagcc | ttgctggtct | gccaccttgt | cctcgccctt | 60 |
| gaagggctcc | agtagccagc | gagggccagc | atggcctccc | ccgccccagc | atgcctgggg | 120 |
| tctctgcttt | catggactgt | ttgtgggtgg | ggtgaggtgg | tcagtgggtcc | tccttgtgct | 180 |
| gtgtctgcct | ggggctgtct | gtgggcaacg | tgggtcactc | cctctgtcgt | ggtgcagctg | 240 |
| gcaccatcag | gtgctgttca | aacccctctg | agccccgagc | tgcttgkgat | ctcatttcaa | 300 |
| ctccatgcag | cccctctagg | gcagttttat | ttccccattt | tacagatggg | aaaagagaaa | 360 |
| ctcagattgc | gtaacatgcc | caaggaagca | ccggyccag | wgtttgyttt | gtttgwtttg | 420 |
| sttttgagga | gsagmctctg | tcaccagggc | tggagwgctg | gag | | 463 |

<210> 138
 <211> 699
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (155)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (656)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (658)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (664)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (678)
 <223> n equals a,t,g, or c

| | | | | | | |
|------------|------------|------------|------------|------------|------------|-----|
| <400> 138 | | | | | | |
| gaatgcggga | ataactgaga | ttagcagaac | tgagctctgg | cagaaggaat | tattcaccac | 60 |
| tcttctcgga | gcaccttcca | taccgtgttg | cctaaccttt | ccaagtagcc | tgcatcctgt | 120 |
| gcccagccta | gttgacacct | tttgccctca | gatantgact | tttggggcac | tgtacatcac | 180 |
| tctcattcgg | catcttttac | ctggtggtgg | tagtgagaga | tagtcgtctt | ctctcttctc | 240 |
| tcctcttgtg | ttctgagcca | aggtacgcag | tttctgggtc | acatctccaa | ccagtctcct | 300 |
| aaagtgtgtt | gaccaaaggt | gttgctgagt | ttgaacacat | tgcatattta | aattgcaata | 360 |
| ggacatgtgg | gtgagcaagt | tagttatttt | gtctctatgg | gacagctttg | ccattctcct | 420 |
| tcttgctctc | ccagtggggc | attctgcctt | ttgttaagca | gtgttctggg | aattatagtt | 480 |
| ctgaattcca | ctgacacaat | ctcctcttcc | caccctccgc | tctcctcaaa | cttgccctca | 540 |
| tggggctaca | ctaccacaaa | ggcacatctc | tccttagggc | tggwgggctt | tgctggsaag | 600 |
| gagaacatga | aagaattgya | tgyasagagy | tccagaagct | tctagacatt | tcctgnctng | 660 |
| ttgnntgcgg | tgggttttct | tgaggcacia | tattgttca | | | 699 |

<210> 139

<211> 950
 <212> DNA
 <213> Homo sapiens

<400> 139
 ggcctctgct cgcgctgcct gctcggagcc gcttgctcgg ctgcctctgg ctgggctccg 60
 cgatcctctc cccaccctc gggcactgct ccgcctccct cccggcgggc tgtccccgca 120
 gtgctccccg acccggcgag ccttcggggc gcgcgtcgt ggtgggtggtt gaggctctag 180
 cgataataaa tgatagagga tacaatgact ttgctgtctc tgctgggtcg catcatgcgc 240
 tactttcttg tgagaccgga gacgcttttc ctgctgtgca tcagcttggc tctatggagt 300
 tactttcttc acaccgacga ggtgaagacc atcgtgaagt ccagccggga cgccgwgaa 360
 atgggtgaagg gcaaggtagc cgagatcatg cagaacgatc gactcggggg gcttgatgtg 420
 ctcgaggccg agttttccaa gacctgggag ttcaagaacc acaacgtggc ggtgtactcc 480
 atccagggcc ggagagacca catggaggac cgcttcgaag ttctcacgga tctggccaac 540
 aagacgcacc cgtccatctt cgggatcttc gacgggcacg ggggagagac tgcagctgaa 600
 tatgtaaaat ctgactccc agaggccctt aaacagcatc ttcaggacta cgagaaagac 660
 aaagaaaata gtgtattatc ttaccagacc atccttgaac agcagatttt gtcaattgac 720
 cgagaaatgc tagaaaaatt gactgtatcc tatgatgaag caggcacaac gtgtttgatt 780
 gctctgctat cagataaaga cctcactgtg gccaacgtgg gtgactcgcg cggggtcctg 840
 tgtgacaaag atgggaacgc tattcctttg tctcatgatc acaagcctta ccagttgaag 900
 gaaagaaaga ggataaagag agcaggtggt ttcacagtt tcaatggctc 950

<210> 140
 <211> 2952
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (3)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (12)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (199)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (2938)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (2952)
 <223> n equals a,t,g, or c

<400> 140
 ccnggagtc tnatggggtg ggtacccag agtggaaacca agctttgggc aggggtgccc 60
 tgggcttacc tgtgagggcc agtgarcccc ctccctytcc cagtggccct actttgccag 120
 cagtgaaccc acccctttcc tgccctgcag cgtaamcatt cccagcctc ctacaggcag 180
 aaaaacacct ccaagctgnc agctgggcca ggccccgccc accaagctgt tttcytaagm 240
 cagcyttccg agcaggctat ttttggccct cgtgacagtg attgatagct gctggraagg 300
 tataaaagca gcttgccctgc gaaggttctt cacactgctc aggggaagagc ytgctacggt 360
 ggactgtgag actcagtgca ctgtcctcct ccacgcgacc ccacgctgga cccctgccc 420
 gaccctccac ccttcggccc ccaagcttcc caggggcttc ctttggactg gactgtccct 480
 gctcatccat tctcctgcca cccccagacc tctcagctc caggtaagag agagcagctg 540
 cccttgggtt tgagacaaaa cacaagggtt ttgtttatatt ttgagggcaa tcccagcct 600
 gaacttgac agcctcccta tgggttagag accagggtct tctgtagagg gctttgcatt 660
 tataaaggga ttcagggtt atttcatgca tttcctacaa catcctggcc aggggtattt 720
 ataaccctgt tttatggatg ggtaagtgga ggccctggaga ggtggccttg ccaaaggctc 780

| | | | | | | |
|------------|-------------|-------------|-------------|------------|------------|------|
| catggtcagt | gcgtggccga | tcctggtttt | aaacccagcc | ttcctctgac | cagtgtttgt | 840 |
| taggttaggt | tctcttatct | gtgcacattc | tgaaacgata | atgataaaat | cttaagcctt | 900 |
| tgggggtttt | aacctgaaca | ggaagaaaag | atcccagcag | tcggagctct | ggtctgggct | 960 |
| ctgtagactt | caaattgtct | tcagggcacc | ggattcctac | aggcagcccc | agaggagtgt | 1020 |
| ggtgacgctg | aggggcggtg | ggacgcatgg | cagggcctca | ccaccaggct | tctgtttccc | 1080 |
| aacagggttg | cacctcctct | cgccagagtg | atgagggtccc | ggcttctgct | ctccgtggcc | 1140 |
| catctgcccc | caattcggga | gaccacggag | gagatgctgc | ttgggggtcc | tggacaggag | 1200 |
| ccccaccctt | ctcctagcct | ggatgactac | gtgagggtcta | tatctcgact | ggcacagccc | 1260 |
| acctctgtgc | tggacaaggc | cacggccccag | ggccaaccca | ggccacccca | caggccagcc | 1320 |
| caggcctgcc | ggaagggccg | ccctgctgtg | tccttgcgag | acatcacccg | acgtttcagt | 1380 |
| ggccagcagc | ccacactgcc | catggctgat | actgtggacc | ccctggactg | gstttttggg | 1440 |
| gagtgccagg | aaaagcagcc | aagccagagg | gacctgccaa | ggaggactgg | cccctctgct | 1500 |
| ggcctctggg | gtccacatag | acagatggac | agcagcaagc | ccatgggggc | ccccagaggg | 1560 |
| aggctctgtg | aagccaggat | gcctgggcat | tccttgga | gaccaccgca | ggatgggcag | 1620 |
| cagagctctg | acctaagaag | ctggactttt | gggcagtctg | cccaagccat | ggcctcccgc | 1680 |
| caccgcccc | gccccagcag | tgtcctcaga | acactctact | cgcacctccc | ggtgatccat | 1740 |
| gaactctgac | ccctccccag | ttaaaggcttc | tgtagagagc | atgctgggtc | tgcattcctt | 1800 |
| ctcgtctcct | cactgggtgt | cactgcccc | ggcaggctct | tgaaggga | atgcttttct | 1860 |
| gcagaggccc | ctgcttgggc | agttcacagt | gagaccgacc | ccctctgaat | atgataacag | 1920 |
| cctgtttcac | atgaggagat | gttaccaatc | ccgttcgctc | tgacccttgc | tggctgatca | 1980 |
| ccttgagcaa | cttacttaac | atctgtgttc | ctcagtttct | catgggtaat | atagggataa | 2040 |
| ttactggcac | ctgcctccca | ggccattctg | acgtgtaacc | gcatatagga | gcccactggc | 2100 |
| tgagtatgta | ccatcatcgc | tgggtgggaa | actggtggtg | ggggtgtgag | ggtagtggg | 2160 |
| gtgtcagccc | cccagtggtt | tcagaacaag | gcctcgggca | ctccaagtc | tgcctcttgg | 2220 |
| ctccaccctt | caaagcccat | gttctgtgag | gccaagaga | acacatggag | tcttagcaaa | 2280 |
| tgcactaatg | tattccgggg | gactgtcacc | tggcaccact | ggggcactct | gctggctaca | 2340 |
| actcatacgt | cctgtggtgg | cattgggaga | gttcccccat | gatgagggcc | aagatagaat | 2400 |
| ctgtaccact | cagtgtctacc | atccccaccc | ctacaccact | tccacacagg | ggcctcatgg | 2460 |
| catggtcagg | gtcccagctg | tgggtgagag | cagggcactg | tccagctgtc | cactggggaa | 2520 |
| gtcaagatgt | cctaaggccc | aggycagggc | atctggagtc | tgaaggacct | tagttcctag | 2580 |
| aggcatctgg | cagcaagaag | gtgaggcatc | agggaaacgg | aatcaggctg | ggactgatca | 2640 |
| gaggtgaagg | gacagagaga | ggagaggagg | aagattgagc | tgggggcaac | agccaagctc | 2700 |
| acctgggcag | gtctctgcca | cctccttgct | ctgtgagctg | tcagtctagg | ttattctctt | 2760 |
| tttttgtggc | tatttttaat | tgctttggat | ttgttaaagt | ttttctgtct | tctgttaagt | 2820 |
| gtgttttctc | tggagataga | atgtaaacca | tattaaaagg | aaaaagtttc | agacaagcaa | 2880 |
| aaaaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | aaaaaaancc | 2940 |
| ccgggggggg | gn | | | | | 2952 |

<210> 141

<211> 776

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (631)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (755)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (761)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (768)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (775)

<223> n equals a,t,g, or c

<400> 141

| | | | | | | |
|------------|-------------|------------|-------------|------------|------------|-----|
| gcagagactt | tggatgagtt | tttagcttct | ggtaggcagt | tagagtaaga | agcataatgc | 60 |
| ctaaatcaac | cagggtttgg | gttttctcaa | ggctgtgttt | cagtctttat | ctaagtcttg | 120 |
| gtgtgtttta | gtccttatga | ggcctgggtg | agtcctttag | cagtctcaac | gaaaaccaat | 180 |
| gccattcctc | cacttttaat | ctccctagta | ccacaaaact | gcttagaaga | ctgtttaagt | 240 |
| tcttcagcct | cttagctgcc | actttttgct | tgatttctct | cagactgtgt | cacttagaaa | 300 |
| tcatcaaata | tctcaagaaa | gaaagtacct | cagattattg | gggtttgttt | tctgcctgtc | 360 |
| ccttctctgt | aagatattag | cccttcaatt | accagctctc | ttagtagcaa | tgaagtctaa | 420 |
| gttttgcttt | gctagcccca | tgagactgcc | aaaagcttta | cttgcttctc | ctgcctgttg | 480 |
| gcagctgctt | tctgcttggc | ttcttcacct | ttctcccccac | actgcttaca | aatcagaaaa | 540 |
| agtctcaaga | ataaaaagcaa | aataaatggg | tgggctcacc | ttactgagtt | tctctcctct | 600 |
| cataaatctt | gractcttca | gtcctggctg | ntttggtagc | tttccaatgg | cttyacatgg | 660 |
| acacttccca | accccggccc | cacgatctgg | cytttcttgg | aagtctcaac | taagcctggg | 720 |
| tctggctata | agctgggtaa | caatctctgg | gaaangggcc | nattttcngg | ataana | 776 |

<210> 142

<211> 702

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (3)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (14)

<223> n equals a,t,g, or c

<400> 142

| | | | | | | |
|------------|------------|-------------|-------------|-------------|------------|-----|
| ctnctatagg | gaangctggg | acgcctgcag | gtaccgggtcc | ggaattcccg | ggcttctttc | 60 |
| ttgtgttgct | gctttctcct | tcccagctct | aaactcccat | ggtgctggag | cagccagaga | 120 |
| agaagtgtta | ctagactgac | cactgctacc | tacagtgagc | cccattctgc | acacagaggc | 180 |
| tgcggactcc | tttttcccaa | tcatagacca | gaatgcttgt | gaaagaagat | gtggctgttc | 240 |
| tgcaggttgg | agctctagga | tcggaagaac | tcatctgtat | cacatatgat | ccagctgaaa | 300 |
| gtccctacaa | actgggccc | ctgtgtcttt | agaagcagct | tccaagggca | ggaagacttc | 360 |
| cagagtgcag | gactgagcgt | gctgctaata | ttgttctggg | cgagagactg | atgagagaga | 420 |
| caagaattat | ggcgcgagaa | aagcagcagc | agcagcagca | agtctgcaga | ggggaatgcc | 480 |
| aaactcgcta | ctgggtgttt | ttttttgttt | tgttttgttt | tgktttgttt | tgktttgttt | 540 |
| gatacagagt | ttcactctgt | cacccaggct | ggagttagagt | gggtgccatct | cagctcattg | 600 |
| caacctctgc | cccctgggtt | caagcaattc | tcctgcctca | gccttycgag | tagctgggat | 660 |
| tataggcatg | tgccaccatg | cctggctaata | ttttgtattt | tt | | 702 |

<210> 143

<211> 798

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (2)

<223> n equals a,t,g, or c

<400> 143

| | | | | | | |
|------------|------------|------------|------------|-------------|-------------|-----|
| gncaaaaagc | aagwtggagt | caattatgkc | caatttayct | wactgtcawa | atttttcaaa | 60 |
| ggcagtttca | aggttactat | tctcatgatt | caacacatcc | tcaaggagtg | agattcagtc | 120 |
| tgtgtaagtg | tatcatgact | ttctataaca | cgccttgtea | tgcactcttc | taccctgcta | 180 |
| gaattggcag | ctggcctcag | ctgggttcta | ccagcagtac | tgccatcacc | tcattcctcat | 240 |
| ctgccccatc | tggtgtttts | gaaccacttg | tgctctctga | aatgcataatg | ttgaagtccct | 300 |
| aaccacctgt | gcctcagaat | gggactatgt | ttggagaaag | ggtttttaaag | aggtacttaa | 360 |
| agwtaaatga | gatcattact | gtgaaccctg | atccaaattg | acttatgccc | ttataagaaa | 420 |
| aggaaatttg | gccacttaca | ctcacagagg | aagaaatcat | ttgaagacac | agagagaaga | 480 |
| gggccgagga | gagaggctct | agagaaacca | acccaatgac | atttcgtctt | ggattttccag | 540 |

| | | | | | | |
|------------|------------|-------------|-------------|------------|-------------|-----|
| ccccagaat | tactggaaaa | tacatttttc | ttgttttaggc | cacccaatct | gtactacttt | 600 |
| gttatggcaa | ccctagcaaa | ctaattgcagt | caccaaccca | gggtgaaaat | gggacattcc | 660 |
| caactctagc | tcttaggcca | agcttatttg | taatagattc | ttgttttcaa | aggatataga | 720 |
| tattgagatt | ctcaatgtat | ttgttaaaat | acattgtttc | ttgttaaaag | caaaaaaaaaa | 780 |
| aaaaaaaaag | gcggccgc | | | | | 798 |

<210> 144
 <211> 566
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (442)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (484)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (535)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (537)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (549)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (564)
 <223> n equals a,t,g, or c

| | | | | | | |
|------------|------------|------------|------------|-------------|-------------|-----|
| <400> 144 | | | | | | 60 |
| ggcagcagct | cgactcactg | caacctccgc | ctcctggggt | caagtgattc | tcttgccctca | 120 |
| gcctcccgag | tagctggggg | tacaggcatg | tgccaccacg | cccagcta | ttttgtactt | 180 |
| ttagtagaga | cggggttttg | ccatgttggc | caggctgggc | tcgaactcct | gacctcacat | 240 |
| gatctgcgca | cctaggcctc | ccaaagtgtt | gggattacag | gtgtgagcca | tcgcacccgg | 300 |
| ccaggcttac | ctctttgtac | ctatttttgt | gaagctgaac | tgaggcctgg | ggtgcttgca | 360 |
| ctgtcttggg | gccctgaaaa | gtccaaggca | cagcagtcga | taaataagcaa | ctaaataaat | 420 |
| gatgataaat | atctaataca | agttcgatga | tagatatcaa | attatatata | taaataatcaa | 480 |
| ataacatcsa | ttgtaaatat | cnaataaaaa | ttagattcct | ttaatttttt | taaagacaca | 540 |
| gtgnccagtt | ctgttgccca | ggctggagtm | cagtggcacg | atcatagctt | actgnanctt | 566 |
| gaactcccna | gcttaagcca | tctnca | | | | |

<210> 145
 <211> 1939
 <212> DNA
 <213> Homo sapiens

| | | | | | | |
|------------|------------|------------|------------|------------|-------------|-----|
| <400> 145 | | | | | | 60 |
| gcccagcccc | tgctccctgc | cttgtcccag | cacettcacg | gagtgttggg | ccaaccaata | 120 |
| gccctgagcc | aatttaacag | tcccctggct | ggttttgagg | ggacagtcct | ttattgtttt | 180 |
| tttccaaaac | cgggcagagg | ggtggcagct | cttgtgcctg | gggtccctgc | cagtccgtgg | 240 |
| accaggcctg | gagactggcc | atctggctcc | gtgcccgttt | cgctctcaca | ttaccccgctc | 300 |
| ctctgcccac | ccacccccaa | gatgccactt | gggtgtctgg | ggtcttgggg | tgcccccaga | 360 |
| agtcttatca | ctgccaccct | cccctacccc | aggccgtcca | ccaactaagc | cagctgccac | 420 |
| ygtgtactcg | gtccgggacc | cttggcgaca | gaagacagcc | tccgagagcg | cgggctccaa | |

| | | | | | | |
|------------|-------------|------------|-------------|-------------|-------------|------|
| gggcaataaa | gcagctccac | tctctctact | tggttctttt | tggttcttgcg | tctccagtec | 480 |
| tgtggcgggg | gccagtgcct | ccccctctct | gggcgtgggtc | tggtccctga | ccctgcaggg | 540 |
| agccctgttg | ccagcgctgt | gggtgggaaa | ggcgactgct | cctgcctggg | ctgcagctgg | 600 |
| gcctgacctg | gctgcaagca | caggtgttgc | tttttggggg | aagggatgtg | tcggggctcg | 660 |
| ggccctgccc | tcagggttct | ccagcaacac | ctaggggtgag | gaggcagctt | ccgctaggcc | 720 |
| acatcattgg | ctcagctcac | gggactgggg | ctctgacggt | ttaggggcgr | ctgtggcatt | 780 |
| gaggggcagg | gcttgccag | tgctcttggc | gtcctctggg | ttccagctgt | ccctgtagcc | 840 |
| ggggcagtg | cggcagcagc | agcccaggct | gggcactgcg | gccatgtaga | gtagaggggtg | 900 |
| gacacagaag | gccaggggca | tgaggccccg | catcacctgg | tagcccacgt | agggccccag | 960 |
| ctccagggct | gctgtggcct | gggctatgtc | tgcaaagctc | gggcagcggg | tgctccagcg | 1020 |
| ccgccagaca | tccacgttga | gcacccgcat | gatgtggtag | ggcacatagg | agctggcgta | 1080 |
| gagggccaca | ccactggcca | ccaacgctgc | cacacgcagc | ttctcgggca | cagtcatgcc | 1140 |
| tgggctgctg | agcacggccc | gcccagaggc | gccgtaggct | gccagcgtga | gcagcagcgg | 1200 |
| cagggcgcag | cccaaccccg | ccagcaccag | gctatacgtc | ctgtaggccg | ccagcccgtg | 1260 |
| gtctgctgtc | cccagacact | tgatgcaggc | ctcgggcctg | gccacgctgc | agttgcccgc | 1320 |
| ccccgtctgc | ggcctcttca | ggtgggagaa | gctgagtgtg | ggcatggcca | gcagggcggc | 1380 |
| caggaccag | ccggcagcgc | tcacggccca | ggcgtgcttg | ggtcgcaggt | ggcttcgggc | 1440 |
| gaagaagggg | tgcacgatgc | ccaggtagcg | gttgaggctg | atgcaggtga | tgaagatgac | 1500 |
| gctgcccagc | aggttgccag | tgaagaggaa | gcgctccagg | cggcacgcgg | cctccccata | 1560 |
| gcgccagtgc | ttggggggat | agaggttagc | ggccagcggg | ggcagcgtca | grgcgcagag | 1620 |
| caggtcgctg | actgccagct | ggacagagaa | gaccacggcg | gggtgccatg | ggcgctgctt | 1680 |
| ccggatgctg | aagcgggtaca | gggccaggcc | attgctggcc | acggccacca | ggaactcaac | 1740 |
| caccagtatg | ggccacagga | agtccccctg | gaacccactg | agtttgtcgt | cggcagctgc | 1800 |
| caagaagttg | gcagggcagg | acttggcacc | cgagacgttg | gctgccatgc | tcccgtgccg | 1860 |
| atcctcagcc | tgtgtctgtc | accagttcc | ccagcccctc | ccccagtcac | cagtggctta | 1920 |
| gtgggccttg | ccccagccc | | | | | 1939 |

<210> 146

<211> 619

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (124)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (128)

<223> n equals a,t,g, or c

<400> 146

| | | | | | | |
|------------|-------------|------------|-------------|------------|------------|-----|
| ggtgataaaa | gtccttccag | tcccatctgt | gtggctgtca | cttcttcttc | ccctgtcctg | 60 |
| ctactccaag | cacagtcatt | cctccaaagt | gctgggttcc | tcctggccca | gccggggcca | 120 |
| ttcnttantg | ggcattatct | ttgcaagtgt | gagagccaga | gaggggcatg | tgtagtatcc | 180 |
| atgctcacaa | acagggtctc | atcctccttt | gtgtgggttc | tgtgtctagc | atgtcatctt | 240 |
| ccttctctgc | cctctgcaac | tgaggaattt | gctgtcttta | tacccaagta | tcacagcagc | 300 |
| agaatggggg | ctgccccatg | ccatgtctct | ggtcatgggtg | gtatcaaagg | caacacctgc | 360 |
| caggacaatg | ctgggttatga | tttctgccgt | ccccctgggac | tggcctcatt | ccttaagagg | 420 |
| caagattaaa | aaaaaataaa | aagccaggca | cgaggggtca | tgcctataat | cccagcactc | 480 |
| cagcactttg | ggaggccaaa | gcgaggatt | gcttgaactc | aggagttcra | gaccagcctg | 540 |
| ggcaacatag | cgagacccca | tctctacaaa | aaatttaaaa | atgaggcagg | tatggaggta | 600 |
| tgcgcctgtg | gttccagct | | | | | 619 |

<210> 147

<211> 2032

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (5)

<223> n equals a,t,g, or c

<400> 147

| | | | | | | |
|-------------|------------|-------------|-------------|-------------|-------------|------|
| tccnctcga | aataacccta | ctaaagggaa | caaaagctgg | agctccaccg | cggtggcggc | 60 |
| cgctctagaa | ctagtggatc | ccccgggctg | caggaattcg | gcacgaggca | acgcgctgtc | 120 |
| catgtcgcgg | gcctcgcctg | gactccctgg | gagatgaggc | cgcgagggtc | cccgcgctc | 180 |
| ctgggtgggtg | tcctgggctg | ctgggcctcc | gtgagcgccc | agaccgatgc | caccccggcg | 240 |
| gtgacgacag | agggcctcaa | ctccaccgag | gcagccctgg | ccaccttcgg | aactttcccg | 300 |
| tcgaccaggc | cccccgggac | tcccagggtc | ccagggccct | cctccggccc | caggcctacc | 360 |
| ccagtcacgg | acgttgctgt | tctctgtgtc | tgtgacttat | ccccagcaca | gtgtgacatc | 420 |
| aactgctgct | gtgatcccg | ctgcagctcc | gtggatttca | gtgtcttttc | tgcctgtctc | 480 |
| gttccagttg | tcacgggcga | cagccagttt | tgtagtcaaa | aagcagtc | ctattcattg | 540 |
| aattttacag | caaaccacc | tcaaagagta | tttgaacttg | ttgaccagat | taatccatct | 600 |
| attttctgca | ttcatattac | aaactataaa | cctgcattat | cctttattaa | tccagaagta | 660 |
| cctgatgaaa | acaattttga | tacattgatg | aaaacatctg | atggttttac | attgaatgct | 720 |
| gaatcatatg | tttccctcac | aaccaaactg | gatatttcta | ctgctgctaa | atatgagtat | 780 |
| ggggttccct | tgcagacttc | agattcgttt | ctgagatttc | cttcgtccct | gacatcatct | 840 |
| ctgtgcactg | ataataaccc | tgcagcgttt | ctgggtgaacc | aggctgttaa | gtgcaccaga | 900 |
| aaaataaatt | tagaacagt | tgaagaaatt | gaagccctca | gcatggcttt | ttacagcagc | 960 |
| ccggaaattc | tgagggtacc | tgattcaaga | aaaaagggtc | ctatcactgt | tcagtccatc | 1020 |
| gtcattcagt | ctctaataaa | aacgctcacc | cgacgggagg | acactgatgt | gctgcagccg | 1080 |
| actctcgtca | acgctggaca | ctttagcctt | tgcgtgaatg | ttgttcttga | ggtaaagtac | 1140 |
| agcctcacat | acacagatgc | aggtgaagtc | accaaagctg | atctctcatt | cgttctgggg | 1200 |
| acagttagca | gcgtagtgg | cccactgcag | caaaagtttg | aaattcattt | tcttcaggaa | 1260 |
| aatacccagc | cagtccctct | cagtggaaac | cctggttatg | tcgtggggct | cccattagct | 1320 |
| gctggattcc | agcctcataa | ggggtctggg | attattcaga | ccacaaatag | atatggacag | 1380 |
| cttactatct | ttcatagcac | aactgagcaa | gactgcttag | cactggaggg | ggtcgggacc | 1440 |
| ccagtattat | ttggttacac | tatgcaatct | ggctgtaaac | taagactgac | tggagctctc | 1500 |
| ccgtgtcagc | tcgtagcaca | gaagggtgaag | agcctgctgt | ggggccaggg | cttcccagat | 1560 |
| tacgtggccc | cttttgga | ttcccaggcc | caggacatgc | tggactgggt | gcccattccac | 1620 |
| ttcatcacc | agtcattcaa | caggaaggat | tctgcccagc | tcccaggggc | tttgggtata | 1680 |
| gaagtgaagt | ggactaaata | cggatccctg | ctgaattccac | aggccaaaat | agtcaatgta | 1740 |
| actgcaaatc | taatttcac | ctcctttcct | gaggccaact | caggaaatga | aaggacgatt | 1800 |
| cttatttcca | ctgcggttac | ttttgtggat | gtgtctgcac | ctgcagaggc | aggcttcaga | 1860 |
| gctccaccag | ccatcaatgc | caggctgccc | tttaacttct | tcttcccgtt | tgtttgacaa | 1920 |
| tgctcagatg | catcagttcc | ttaatataca | cgtgaaat | gaaaactgta | cattcgggtga | 1980 |
| gattaaattt | tatatacaac | tarmaaaaaa | aaaaaaaaaa | aaaggctcgac | gc | 2032 |

<210> 148
 <211> 1048
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (965)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (1024)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (1026)
 <223> n equals a,t,g, or c

| | | | | | | |
|-------------|------------|-------------|-------------|------------|-------------|-----|
| tggtgaatg | ggtttgatag | ttgtgcttct | atttcccaac | ctctgtatgt | gtacctttca | 60 |
| tgcagggtgga | tttcagtgtg | ttctttggat | ggcaggcctt | aagagaagag | tcccactgca | 120 |
| cagcctcaga | tacttcatct | ccatgggtggg | tctcttctcc | aaaccaggac | tgcttcccgt | 180 |
| gtatgccaga | aatccaccag | gatggtcaca | gctctttctg | ggcacagtat | gtaaggggaga | 240 |
| tttcacccgt | gtgatagcca | cgaaatgtca | gaaaggacaa | aaaagtcaga | agaaaccaag | 300 |
| ccatcttgga | ccactagatg | gttcctggca | ggaaaggctg | gctgatgttg | tgacaccact | 360 |
| ctggagggtg | agctatgaag | aacagctcaa | ggtgaaat | gcagctcaga | agaaaatttt | 420 |
| acaaagacta | gagtcttaca | tccaaatgct | caatggagtc | agtgtgacaa | cggctgtacc | 480 |
| caaatctgag | aggctctctt | gtcttctcca | tcctattata | cccyctcctg | tcatcaatgg | 540 |
| ttaccgaaat | aagtccacct | tctctgtgaa | ccgagggtcca | gatggcaatc | caaagactgt | 600 |

| | | | | | | |
|-------------|------------|------------|-------------|------------|-------------|------|
| ggggtttctac | ctgggaactt | ggagagatgg | gaacgttgctc | tgtgtgcagt | ctaatacatct | 660 |
| gaaaaacatc | cctgagaaac | acagtcaagt | ggcgcagtac | tatgaagtat | tccttcgaca | 720 |
| gtctcattg | gagccctgcc | ttgtatttca | tgaagggtgga | tactggcgk | agctcacagt | 780 |
| ccgcaccaat | agccaagggc | acacaatggc | tatcatcact | ttccatcccc | agaaattaag | 840 |
| tcaggaggag | ctccatgttc | agaaggagat | tgtaaaggaa | tttttcatca | agaggctctg | 900 |
| gagcagcctg | tggcttgacc | tcactttact | tccaggaaaag | taccatgacc | cgttgcaacc | 960 |
| atcancagtc | tcctatcaa | gcttctgttt | ggggaaccta | catcttttga | agaacttctg | 1020 |
| agcntngaaa | gatccggatc | tctccaag | | | | 1048 |

<210> 149

<211> 701

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (691)

<223> n equals a,t,g, or c

<400> 149

| | | | | | | |
|------------|-------------|------------|-------------|------------|------------|-----|
| gcttaattct | cctgagaaca | tgacatcacg | caaggctaca | tggagataaa | tctcttgaag | 60 |
| agcaaactgt | caggaaatgt | ccaacacaaa | tggcagtgca | atcacagaat | tcattttact | 120 |
| tgggctcaca | gattgcccgg | aactccagtc | tctgcttttt | gtgctgtttc | tgggtgttta | 180 |
| cctcgctcac | ctgctaggca | acctgggcat | gataatgtta | atgagactgg | actctcgctt | 240 |
| tcacacgccc | atgtacttct | tcctcactaa | cttagccttt | gtggatttgt | gctatacatc | 300 |
| aaatgcaacc | ccgcagatgt | cgactaatat | cgtatctgag | aagaccattt | cctttgctgg | 360 |
| ttgctttaca | cagtgtctaca | ttttcattgc | ccttctactc | actgagtttt | acatgctggc | 420 |
| agcaatggcc | tatgaccgct | atgtggccat | ataagaccct | ctgcgctaca | gtgtgaaaac | 480 |
| gtccaggaga | gtttgcatct | gcttggccac | atttccttat | gtctatggct | tctcagatgg | 540 |
| actcttccag | gccatcctga | ccttccgect | gaccttctgt | agatccaatg | tcataacca | 600 |
| cttctactgt | gctgaccgcg | cgctcattaa | gctttctgtt | gtctatgcaa | gacatgcatg | 660 |
| tmattstgct | gaactctcag | tcctacatcg | ntggggccagc | t | | 701 |

<210> 150

<211> 617

<212> DNA

<213> Homo sapiens

<400> 150

| | | | | | | |
|-------------|-------------|------------|------------|------------|------------|-----|
| acgtgaaaaat | ctgcctttctc | accatgaggc | ttctagtctt | ttccagcctg | ctctgtatcc | 60 |
| tgcttctctg | cttctccate | ttctccacag | aagggaagag | gcgtcctgcc | aaggcctggt | 120 |
| caggcaggag | aaccaggctc | tgctgccacc | gagtccttag | ccccaactca | acaaacttga | 180 |
| aagccttcac | agcagtgagc | tgcaatgttg | gagggcttca | tctcgggctg | caaggaccct | 240 |
| gggaaagttc | cagaactcca | cgtccttgct | tcaattgtgc | catcaacttt | cagagctatc | 300 |
| atgagccaac | ctcacccac | agggcctcag | tcgccaccat | gtgggcctct | ccagtgcaaa | 360 |
| ccaccgagca | ttccaccatg | accggtcaca | gctacaaatc | cagagaccat | caatcctgct | 420 |
| agagtgcagg | gtggcaagca | cccaagggtg | gctgaccaag | actgcagagt | ctcctccatc | 480 |
| ttcaggtcca | ttcagcctcc | tggcatttaa | ctaccagcat | ccagtggkcc | ccaaggaatc | 540 |
| ccttcttagc | ctcctgacat | gagtcgtctg | gaaagagcat | ccaaacaaac | aagkaataaa | 600 |
| taaataaata | aactcaa | | | | | 617 |

<210> 151

<211> 881

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (864)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (869)

<223> n equals a,t,g, or c


```

<400> 151
gccacgcgt ccgcacagct cccttcccag gacgtgaaaa tctgccttct caccatgagg      60
cttctagtcc tttccagcct gctctgtatc ctgcttctct gcttctccat cttctccaca      120
gaagggaaga ggcgtcctgc caaggcctgg tcaggcagga gaaccaggct ctgctgccac      180
cgagtcccta gcccgaactc aacaaacctg aaaggacatc atgtgaggct ctgtaaacca      240
tgcaagcttg agccagagcc ccgcctttgg gtggtgcctg gggcactccc acagggtgtag      300
cactcccaaa gcaagactcc agacagcgga gaacctcatg cctggcacct gaggtaccca      360
gcagcctcct gtctcccctt tcagccttca cagcagttag ctgcaatgtt ggagggcttc      420
atctcgggct gcaaggaccc tgggaaagt ccagaactcc acgtccttgt ctcaattgtg      480
ccatcaactt tcagagctat catgagccaa cctcacccca cagggcctca gtcgccacca      540
tgtgggcctc tccagtgcaa accaccgagc attccaccat gaccggtcac agctacaaat      600
ccagagacca tcaatcctgc tagagtgcag ggwggcaagc acccaagggg ggctgaccaa      660
gactgcagag tctctcccat cttcagggtc attcagcctc ctggcattta actaccagca      720
tccagtggtc cccaaggaat cccttcctag cctcctgaca tgagtctgct ggaaagagca      780
tccaaacaaa caagtaataa ataaataaat aaactcaaaa aaaaaaaaaa aaaaaaaaaa      840
aaaaaaaaaa aaaagggcgg ccgntctana ggatccaagc t                                881

```

<210> 152

<211> 576

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (436)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (488)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (510)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (531)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (551)

<223> n equals a,t,g, or c

<400> 152

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ggacgcagcc aggttgtccc agctttcgct ctacgcgcag cgcgaggagc gcgatgtctg      60
ggctgtctcg cccgtgtctt ttggccgtcg gctgcctggc cgcgctctgc gtaatcacag      120
cggctgggaa caccaccctg gccccgaacg tgactacagc ctcgctctcca ccgccacca      180
ccacgcagct cccggtgtca ccgacgactc tctcgccgct gccggtcacc actccagcac      240
cagatatctg tggaagccga aacagttgtg tttcctgtgt tgatggtaat gctacctgct      300
tttggataga atgtaaagggt aaaagctact gttcagataa ttcaacagct ggtgattgca      360
aggtgggtgaa caccacagga ttctgttctg ctaaaaccac aactctgcct tccactacta      420
caacttccac cacagntact acatcaggta caactaatac cactctatct ccaactatac      480
aacctacncg gaagtctacc tttgatgcan gccagtttca ttggaggaat ngcccttgct      540
tgggtgtgca ngctgtaatt ttctttctct attaatt                                576

```

<210> 153

<211> 637

<212> DNA

<213> Homo sapiens

<400> 153

```

ggcagagcc caggctcaag caatccttct gccttgacct cccaagggtc tgggattaca      60

```

| | | | | | | |
|-------------|------------|------------|------------|------------|------------|-----|
| ggcatgagcc | gctgcacctg | gccttcattt | agtttctttt | tttcttcctt | tctttctttt | 120 |
| tttagatgga | gtctcgctct | gtcagccagg | ctggagggca | gtggcgatg | cttggctcac | 180 |
| tgcaacctcc | gcctcccagg | ttcaagcgat | tctcctgcct | cggcctccca | aagtgctggg | 240 |
| attacaggca | tgagccgctg | tgctgacgtt | catttgggtt | ctataatcac | caaagcccat | 300 |
| ctgggtctcat | ggcccttgca | gatgaatatc | ctcccttaga | acacatcttc | ccaagagtt | 360 |
| caccctgatg | gcaacttctc | atccattagg | cctcagcttt | aatgtatcat | cttcagggat | 420 |
| gctttcactg | tccctccctt | ccagtgtaat | ctagatccct | gtctctatta | cccagcactg | 480 |
| tcaacagata | gaaatgttcc | ctatctgtcc | tgtccaatat | tacagccacc | actgtatgtg | 540 |
| gtcagtgagc | acttgaaatg | tgaactgaat | tttaagattc | gatttaatat | taattttatt | 600 |
| aaatgtaaac | aaccacatgt | ggccagtggc | taccaga | | | 637 |

<210> 154
 <211> 800
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (4)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (19)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (61)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (100)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (150)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (156)
 <223> n equals a,t,g, or c

| | | | | | | |
|------------|------------|------------|------------|-------------|------------|-----|
| <400> 154 | | | | | | |
| aagnaatgga | atcaaagant | aattttcttg | gtctctgtgt | ctctgggtctt | ctcctaagtc | 60 |
| ntggagcttg | aaaatctgcc | gcagaatggc | cgccagtgtg | acagtgcag | gggaacagca | 120 |
| cccatggatg | ctcctctgaa | gagactttcn | tcattnactg | ccgaggcccc | atgaawcaat | 180 |
| gtctggtasc | caccggwayt | masgaaccgr | aaaaccmaag | ctatatggta | agaggctgtg | 240 |
| caaccgcctm | aatgtgcmma | matgccmacc | tgggtgacgc | cytcagcatg | aaccacattg | 300 |
| atgtctcctg | ctgtactaaa | agtggctgta | accaccagca | cctggatgtc | cagtaccgca | 360 |
| gtggggctgc | tcctcagcct | ggccctgccc | atctcagcyt | caccatcacc | ctgctaata | 420 |
| ctgccagact | gtggggaggc | actctcctct | ggacctaaac | ctgaaatccc | cctctctgcc | 480 |
| ctggctggat | ccgggggacc | cctttgccct | tcctctggct | cccagcccta | cagacttgct | 540 |
| gtgtgacctc | aggccagtgt | gccgacctct | ctgggcctca | gttttcccag | ctatgaaaac | 600 |
| agctatctca | caaagtgtgt | tgaagcagaa | gagaaaagct | ggaggaaggc | cgtgggcca | 660 |
| tgggagagct | cttgttatta | ttaatatgtt | tgcgcgtgtt | gtgttggtgt | tattaattaa | 720 |
| tattcatatt | atttatttta | tacttacata | aagattttgt | wccagtga | aaaaaaaaa | 780 |
| aaaaaaaaa | aaaaactcga | | | | | 800 |

<210> 155
 <211> 684
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (668)
 <223> n equals a,t,g, or c

<400> 155
 ctactaaag ggaacaaaag ctggagctcg cgcgcctgca ggtcgacact agtggatcca 60
 aagaattcgg cactgagctc tctctctctc cttttttttt acagggtatt actctatgcc 120
 caggctggag tgcagtagct caatctcagc tcaactgcagc tggactcaag 180
 cagtcctccc accccagcct cccaagtagc tgggactaca gatactcaac accacaccg 240
 gctaattttt ttgtagagat ggaatttcac catgttgccc aggctggctc cgaactccta 300
 ggctcaggcg atctgcccac ctcaacctcc cacagtgtcg gtattacagg cgtgaagcca 360
 ccacgccccca ccaagattga tttcttctga ggggtctctt cttggccatc ttctgtgtct 420
 tcccatgggtc ttccctctgt tatgctgtt tgctctgatt tcttcttctc tggctgggtga 480
 ggaggccggc gggctccggg tccagaagct ctggccggct gttgktctga gccatctgcc 540
 ggtctgtctg tttcactgct ctggaatctg gagtggagtc attgagctga aggttggatg 600
 ggagggacat gktctcccg ggcaggcgca cgttgktgag ttttaagggtg tggagcactt 660
 gatatcanaa atgggtgccc gcgg 684

<210> 156
 <211> 1574
 <212> DNA
 <213> Homo sapiens

<400> 156
 acacagtgtc aggaggttta aagggtgtaa tgtgttggtc acatcacaac cagtaagaaa 60
 cgcttggtag gttatccaca tcttttgctg actgtttcca tatacaattc tggtcaccgt 120
 attttccaaa gctaaaatct gaggcgtggg ctgatggttt ttgaaatcag gattacccca 180
 ggaagaacca ggtcctatta ctaattttcc tgattctgag gctctgaagg cttgtctgag 240
 acacattccg gagacctttg taccagaact tggatgcata gtccacctta ctactgatac 300
 acgcctgagc acccttttagg gcgaggcgcc gcctcctgcc tgctgtcctg tccctcagca 360
 tcagaagagt tgaattcagc aggagacggg agcccgggtg ccatgaggga agaggggtcg 420
 cgcttggttt ctactgacct ccatgaagat ttcagacttg cagtgcggcc acctggccct 480
 gccctgcctc tctctttctc atacagcttt aaaactttac tacttttatt taaaaatgaa 540
 ctggatggga gagaagtagc gtcccctacc ctacaagtca cacattccgg ggakgggggt 600
 ggggggtgga ggcaggaagt catgggggtg ggggtgggag cacgggaaca gctttcttaa 660
 ggcctcaggg tctgttttcc cctggcctct tctagagggc ccgtggacag gtcgcagtgc 720
 gtgcttattt ggaaaccagg tgtgtgagcc gaatgcctgc caggccatgc actcagcaga 780
 ggagcccttg tacctggctg ccctgagagg agcaagaggc cacctcccat gtggctctag 840
 acaccacgtg ggctcattag cccagcgtc tgtgccggct ccagggtgct gcctctgggt 900
 gtgtgagtg gagactttgc tccctggcct catcctagag aggcccctgg tgcctagtgc 960
 tgaggcctct ggggctggaa agcctcagca gaaaggaggc actactgagc aactatgcat 1020
 tgtcattgtc ggggtttggg ctttcgggtg ttccttggtg actgggaatt gcttgtgtgc 1080
 atgtgttggg tgcattgttc cgggtctcag ctgcccagc cccgcacagg caacccttc 1140
 ccatccaaag ccattggtg agcttctctg gaatcatttg ccaaaagccc aaggcagaat 1200
 ccaagggtcc aagaccattt ccatggagct catgttttct ttttctgtag gaactttttt 1260
 ttaaccagca cccaccataa ttccgaagc caggtttcat ctttctgga tcactacagt 1320
 gaagtattac agttgtacag ttcccagtc ggccttggtc tgctcggata aaactttgta 1380
 tgtattttgt atggcataga ttctatatg taatgatgtc ctatgcaaaa agaaaaatta 1440
 acgaaattgt aaattttatt gttttaacgt gtatgcatgt ttagtgacgt ttacattttg 1500
 aaataaaatt tatgattcat taaaaaaaaa aaaaaaaaaa aaaaaaaacy cgaggggggg 1560
 cccggaaccc matt 1574

<210> 157
 <211> 2050
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (878)
 <223> n equals a,t,g, or c

<220>
 <221> SITE

<222> (1573)

<223> n equals a,t,g, or c

<400> 157

| | | | | | | |
|------------|-------------|-------------|-------------|-------------|------------|------|
| ggcagcagtg | atgctccagt | ggcaggagca | actcaagttc | atcattgtcc | tgagagagag | 60 |
| gagcagcgcg | gttctcggcc | gggacagcag | aacgccaggg | gaccctcacc | tgggcgcgcc | 120 |
| ggggcacggg | ctttgattgt | cctggggctg | cggagacccg | cgcgctgcc | ctgcacgccg | 180 |
| ggcggcaacc | tttgagctcg | cggtggctgc | tgcatcgccg | cggcgggtcc | ctgccgaagg | 240 |
| ctcggctgct | tctgtccacc | tcttacctt | cttcatttat | cgggtggatca | tttcgagagt | 300 |
| ccgtcttgta | aatgtttggc | actttgctac | tttattgctt | ctttctggcg | acagttccag | 360 |
| cactcgccga | gaccggcgga | gaaaggcagc | tgagcccga | gaagagcgaa | atatggggac | 420 |
| ccgggctaaa | agcagacgtc | gtccttccc | cccgtatatt | ctatattcag | gcagtggata | 480 |
| catcagggaa | taaattcaca | tcttctccag | gcgaaaagg | cttccagggtg | aaagtctcag | 540 |
| caccagagga | gcaattcact | agagttggag | tccaggtttt | agaccgaaaa | gatgggtcct | 600 |
| tcatagtaag | atacagaatg | tatgcaagct | acaaaaatct | gaagggtggaa | gttaaattcc | 660 |
| aagggcaaca | tgtggccaaa | tccccatata | ttttaaaagg | gccggtttac | catgagaact | 720 |
| gtgactgtcc | tctgcaagat | agtgcagcct | ggctacggga | gatgaactgc | cctgaaacca | 780 |
| ttgctcagat | tcagagagat | ctggcacatt | tccctgctgt | ggatccagaa | aagattgcag | 840 |
| tagaaatccc | aaaaagattt | ggacagaggc | agagctantg | tcactacacc | ttaaaggata | 900 |
| acaaggttta | tatcaagact | catggtgaac | atgtaggttt | tagaattttc | atggatgcca | 960 |
| tactactttc | tttgactaga | aagggtgaaga | tgccagatgt | ggagctcttt | gttaatttgg | 1020 |
| gagactggcc | tttggaaaaa | aagaaatcca | attcaaacat | ccatccgayc | ttttcctggt | 1080 |
| gtggctccac | agattccaag | gatatcgtga | tgcttacgta | cgatttgact | gattctgttc | 1140 |
| tggaaaccat | gggccgggta | agtctggata | tgatgtccgt | gcaagctaac | acgggtcctc | 1200 |
| cctggggaag | caaaaatttc | actgccgtct | ggagagggcg | agacagccgc | aaagagagac | 1260 |
| tcgagctggg | taaactcagt | agaaaacacc | cagaactcat | agacgctgct | ttcaccaact | 1320 |
| ttttcttctt | taaacacgat | gaaaacctgt | atgggtcccat | tgtgaacata | tttcattttt | 1380 |
| tgatttcttc | aagcataagt | atcmaataaa | tatcgatggc | actgtagcag | cttatcgctt | 1440 |
| gccatatttg | ctagttgggt | acagtgttgt | gctgaagcag | gattccatct | actatgaaca | 1500 |
| tttttacaat | gagctgcagc | cctggaaaca | ctacattcca | gttaagagca | acctgagcga | 1560 |
| tctgctagaa | aanccttaaat | gggcgaaaga | tcacgatgaa | gaggccaaaa | agatagcaaa | 1620 |
| agcaggacaa | gaatttgcaa | gaaataatct | catgggcat | gacatattct | gttattattt | 1680 |
| caaacttttc | caggaatatg | ccaattttaca | agtgagtgag | ccccaaatcc | gagagggcat | 1740 |
| gaaaagggta | gaaccacaga | ctgaggacga | cctcttccct | tgtacttgcc | ataggaaaaa | 1800 |
| gaccaaatga | gaactctgat | atgcaaaaata | acttctatta | gaataatggg | gctctgaaga | 1860 |
| ctctgactta | ctaaaaagaa | gaattttttt | aagtattaat | tccatggaca | atataaaatc | 1920 |
| tgtgtgattg | tttgagctat | gaagacacat | ttctacttat | gcagtattct | catgactgta | 1980 |
| ctttaaagta | cattttttaga | atttttataat | aaaaccmctt | ttatttttaa | aaaaaaaaaa | 2040 |
| aaaaaaaaaa | | | | | | 2050 |

<210> 158

<211> 638

<212> DNA

<213> Homo sapiens

<400> 158

| | | | | | | |
|-------------|-------------|------------|-------------|------------|-------------|-----|
| ggtgacagag | agatactctg | tctcttaaaa | gaaagaaaaa | gaaaaaagag | aagggggatc | 60 |
| tgtggcaaga | gctggaaaagt | ccccagacag | ctctgaggta | ccgcctctca | tgggctccgt | 120 |
| ggattatctc | atggcctgtg | tggctgtctg | tctttatctc | tagtgacatc | tctgcttttc | 180 |
| tctgccaaaga | tttatccctt | ctctgcagcc | acttgctgtc | cagcttccct | tctttgtaga | 240 |
| atctgcctct | gccaataacc | tttacttttc | tgtggcctct | ctgggctcct | ccatatcatg | 300 |
| acctgkcagc | tcctctttta | ctcctttctt | ctctcaagtg | tttctcagat | cagagaccag | 360 |
| attgcaatga | gagaatcagt | ttggtctggg | agtattttcac | gccaaaaaga | gttgggtcacc | 420 |
| ctttggatta | tatgcctttg | gttcaggcgc | ctacccttgg | tcctggctgt | tggggatgga | 480 |
| tggtgactgk | tatgtggcct | ttacaggcct | taggcacaat | aaagctttcc | caggttcagc | 540 |
| ctactgagtg | ctatggctat | gacctggaca | ttaaactggc | cctcataggt | tcagacctgg | 600 |
| ccatggcaat | tgacgaaccc | taccacaggg | ctcttggga | | | 638 |

<210> 159

<211> 1332

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (11)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (50)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1323)

<223> n equals a,t,g, or c

<400> 159

| | | | | | | |
|------------|------------|------------|-------------|------------|-------------|------|
| gccgggattt | ncaggtgtra | gccmccatgc | ccagcccttt | tcaatattgn | ttttgaaaat | 60 |
| tccatcctat | actgccaaat | ataaatatat | cccaagaaat | taaaatacag | aaaatcaaat | 120 |
| tgcaaagaaa | atatggttgc | agaattcctg | caattttaatt | ttagtaaatt | ctttatcttt | 180 |
| tttattacca | taccttaaaa | ttgctatgca | catattttct | gtctcagtta | tgtactcaac | 240 |
| tagaaattac | ctttacttwa | ctacctgtat | tttattgaaa | tactgtgccc | atcctgcatg | 300 |
| gactattttg | cgtcacttat | tttatgaata | tcactattgg | atatgctctt | ttgcaccaat | 360 |
| agactcttat | tcaggtatga | cacacagaga | cacaaaatgc | taaattctcc | tttcctgtga | 420 |
| ccatggcaga | aactactaat | caatattctt | gggcaaagtt | ggttctcaag | atgctcaagc | 480 |
| tctgctgttg | tcataaagca | ttttggttct | cttctgatac | tttttgaaga | ctcatccatt | 540 |
| tttcattctt | tcagcaaaca | tgaccatgat | accccatata | gaccagatat | tgtgctacag | 600 |
| ttgcgaaaaa | aaagaataag | agaggtcctc | aagcggctca | acatctcatg | gtgaaaatga | 660 |
| gatgctgagc | caccactaac | atgctagctg | ttaagtatgt | ccacttaaaa | gagaacacag | 720 |
| gagaaacatc | tcaggcggac | tctgttggcg | tggttgggtg | tgagggaatg | ttgaagagtg | 780 |
| gatagaggta | taattaaagg | ctttctggat | ggcgtgggtg | cttatatgag | tagtcccagc | 840 |
| actttgggtg | ggattacagc | acttgaggtc | aagagctgga | gatgtgcctg | gccaacacgg | 900 |
| tgaaacccca | tctctactaa | aaatacaaaa | attagcagct | gagcgtggta | gtgtggcgcc | 960 |
| cgcaatgcca | gcccacacgg | aggctgaggc | atgagaatca | cttgaactca | ggaggtggaa | 1020 |
| gtctcagcgg | gcccagatcg | caccactgca | ctccagccag | ggtgatgaag | cgagactctg | 1080 |
| tcaatcaaac | aatcaatcaa | tcaatcaatc | aatcaaggct | tcccaagggg | gaggaatctg | 1140 |
| gcatttttgt | aggcaaagga | aacagcttat | aagatgtgag | agaacacagc | catttttagag | 1200 |
| aagtgtactc | gtgccgaatt | cctgcagccc | gggggatcca | ctagttctag | agcggccgcc | 1260 |
| accgcggtgg | agctccagct | tttgttcctt | ttagtgaggg | ttaatttcgm | gmwggggtaa | 1320 |
| tcnegctatc | at | | | | | 1332 |

<210> 160

<211> 1267

<212> DNA

<213> Homo sapiens

<400> 160

| | | | | | | |
|-------------|------------|------------|------------|-------------|-------------|------|
| cggtgtttg | gctgctgaca | acatgaagac | ttcctgcat | gagaacagag | gcacaggtgc | 60 |
| cggccctaca | gccccagaa | cctggactgg | agggggccat | ggggcaccgg | accctggtcc | 120 |
| tgccctgggt | gctgctgacc | ttgtgtgtca | ctgcggggac | cccggagggtg | tgggttcaag | 180 |
| ttcggatgga | ggccaccgag | ctctcgtcct | tcaccatccg | ttgtgggttc | ctggggctctg | 240 |
| gtcccatctc | cctggtgact | gtgagctggg | ggggcccga | cgggtgctggg | gggaccacgc | 300 |
| tggtgtgtgt | gcaccagaa | cgtggcatcc | ggcaatgggc | ccctgctcgc | caggcccgcct | 360 |
| gggaaaccca | gagcagcatc | tctctcatcc | tggaggctc | tggggccagc | agcccctgcg | 420 |
| ccaacaccac | cttctgtctg | aagtttgcgt | ccttccttga | gggctcctgg | gaggcctgtg | 480 |
| ggagcctccc | gcccagctca | gacccagggc | tctctgcccc | gcccactcct | gcccccatte | 540 |
| tgcgggcaga | cctggccggg | atcttggggg | tctcaggagt | cctcctcttt | ggctgtgtct | 600 |
| acctccttca | tctgtctgcg | cgacataagc | acgcctctgc | ccctaggctc | cagccgtccc | 660 |
| gcaccagccc | ccaggcaccc | agagcacgag | catgggcacc | aagccaggcc | tcccaggctg | 720 |
| ctcttcacgt | cccttatgcc | actatcaaca | ccagctgccg | cccagctact | ttggacacag | 780 |
| ctcaccacca | tggggggccg | tcctggtggg | cgctactccc | caccacagct | gcacaccggc | 840 |
| cccaggggccc | tgcgccttgg | gcctccacac | ccatccctgc | acgtggcagc | tttgtctctg | 900 |
| ttgagaatgg | actctacgct | caggcagggg | agaggcctcc | tcacactggg | cccggcctca | 960 |
| ctcttttccc | tgaccctcgg | gggcccaggg | ccatggaagg | acccttagga | gttcgatgag | 1020 |
| agagaccatg | aggccactgg | gctttccccc | tcccaggcct | cctgggtgtc | atccccctac | 1080 |
| tttaattctt | gggcctccaa | taagtgtccc | ataggtgtct | ggccaggccc | acctgtctcg | 1140 |
| gatgtgggtc | gtgtgcgtgt | gtgggcacag | gtgtgagtg | gtgagtgaca | gttaccat | 1200 |
| ttcagtcatt | tcctgctgca | actaagtcag | caacacagtt | tctctgaaaa | aaaaaaaaaa | 1260 |
| aaaaaaa | | | | | | 1267 |

<210> 161
 <211> 476
 <212> DNA
 <213> Homo sapiens

<400> 161
 ggagactcta gatccagacc cacatggcac ggggctgcct ccctcaggca gttctcagcc 60
 agggcccccac ccagggcaca ggctcaggct gagcgggggtg gtggatgggc tggagccggg 120
 gagaagggca gcaaggctgg ctggccgcag ccctctgttg ctggacacga cttggcaagg 180
 ccgaggggatc tgagggctgg gctactctcg agggctgccca gggtcccagc ttgctgcagg 240
 gaaatgaagg ggggtgccgc ctgaacaggc acatgcctaa gcaagggtatt gacgcttgga 300
 taaagctggc aaccaccagg agaagccttt ttgggatttt tcaaatacctt cgycatccga 360
 gctgtgatga tggagtggar cgtkgcacgg gccatttga gttctgtkkg ctccatcggm 420
 actarcaggg atttgrackt caggctgggtg ggccttgtag gaagcctgct ccctgc 476

<210> 162
 <211> 1040
 <212> DNA
 <213> Homo sapiens

<400> 162
 tcgaccacag cgctccgccc cgctccgcm gggagtagga gaatgtcttc cagaaaaata 60
 cataagctag tttctgttct gtaaagtgat atctttcata cttgaccaa gttcccaata 120
 acttcccaac cactgttcaa aagctgtgat ttttgtctcc ctttcccacc ctccagccaa 180
 ggagcagccc tgcccagggg gcattaggtg tgggtaccgc gggagcacc cgttcctgga 240
 cccagtggtt gcatttcctg gctgaggaag ggtggtcatc ccagctcctg ccctaccctc 300
 tcaacttaact ggagcttttg gacgcaccct ccacagtggg aggtggtggt ggggtggcgtt 360
 ggcggggcct cagcacagct tgggtgctggt aagaggaagc ccgtggttct ggctaggctc 420
 tcatgtccag acagcgggga ccaggggaaa acccagcccc ttctgtaatc ccccttcatt 480
 tectacettc cttctctctc tgtttagcaa aggagggcag ctcacttgga tgtccttaca 540
 acgccccttg ccccaggttg agcaataaga aaccagaacc ttgcggccca gtggcccggg 600
 ccagttcagc ccgctcccc ctctctgcc tggggccatt gagcccagcc tccagggccc 660
 ggggtgcgtt gcaggccagt ggccactgtc cgggctgtga tggcaccaag gcaggtggag 720
 caccaggtac cacacagctg ggcttcccac caggctttcc cgcggggggtc tcagggagct 780
 tctccccagc gctgctcgga gtctgcagga actggccttg ttctccttag cccgtcactc 840
 catacagtat taggtgagga tggatgcggg cgctgtcctt gccgggaagt cactgttgaa 900
 gttgcagtgg cttgttcaca cctgtgggaa gagaagtga gactttctcc ttgcattaaa 960
 aagtctgaac tgtgaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaagaggt 1020
 tctagatcgc gagcggccgc

<210> 163
 <211> 621
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (4)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (8)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (24)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (60)
 <223> n equals a,t,g, or c

<220>

<221> SITE
 <222> (119)
 <223> n equals a,t,g, or c

<400> 163
 gagnggggnag ctcgggggaa gggncctcgc agagaaacag aagaacatgg gctgtggggg 60
 accttcagca gcccggggtt ccaatcccag ctctcccatg tgggagccaa gcaccccang 120
 cagcctttcc cagccttgct tagggccggg ttgggagaat cccaccccg cagggtgtgg 180
 tgagggttga acggagggtg tgtggtgagg gttgagcgga ggggtgtgtga tgcgtggtga 240
 ggggttagca ataagaaacc agaacccttg agcctccagg gccraatgc gtttgcaggc 300
 cagtggccac tgtccgggct gtgatggcac caaggcagg ggagcaccag gtaccacaca 360
 gctgggcttc ccaccaggct ttcccgcggg ggtctcagg agcttctccc cagcgctgct 420
 sggagtctgc aggaactggc cttgttctcc ttagcccgct actccataca gtattaggtg 480
 aggatggatg cgggcgctgt ccttgccggg aagtcactgt tgaagttgca gtggcttggt 540
 cacacctgtg ggaagagaag tgaagacttt ctcttgcat taaaaagtct gaactgagaa 600
 aaaaaaaaaa aaaaaactcg a 621

<210> 164
 <211> 601
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (592)
 <223> n equals a,t,g, or c

<400> 164
 ggagaacags tgacggtctt tccataagt cttctaagag agatgtgtgg taccgccggg 60
 taagtakaca gcaactgagc cctccctccc accccaggy tcccagagca acagggagca 120
 ggagcatag gacctggccg sagccaggaa tctacactga cgggtcagc ccatgaagta 180
 tcttgggctg aagtcacagg atgagactgt ttgtatctgt aactgtcctt gtcattctgtc 240
 ttgcagattt agaagaggaa tcagaaagct gggacaactc tgagtctgaa gaggaggaga 300
 aagccccctgt gttgccagag agtacagaag gggcgaggct gaccagggc ccggcagagt 360
 cctcctctct ctcaggctgt gggagctggc agccccggaa gctgccagtc ttcaagtccc 420
 tccggcacat gaggcaggta ggcggcagg gcacagcgca tcaggagctc aggaggagag 480
 ccaatcatgg gctgtccctg cccacacgce ttgcctctgg accctccacc ttcaaaaccc 540
 tgcaggaagt gactgacagc ctctcgggtg ggtggctgag ggcacagggc gntgggggta 600
 t 601

<210> 165
 <211> 3337
 <212> DNA
 <213> Homo sapiens

<400> 165
 attatattag tcttggctct tttagaaact agtttgcttc atcactttgc tggcttctca 60
 cagatttcta aaagcaattc ccaggctatt gtgggctatg gtttgatgat attacttata 120
 atactgtgga tacttagaga aattcaaagc atatatatca ttggaatttt ccgaaatccc 180
 ttttatccga aggatgtgca aactgtgact gtattctttg agaagcaaac taggctcatg 240
 aagattggta ttgtcagacg gatatttgcta acttttagtat cactttttgc catgatagca 300
 tttctttcat tggacagttc cttacaaggg ctccactcag tgtctgtctg tattggattc 360
 acaagagcct ttagaatggt wtggcagaat wcagaaaawg cyttattgga gacmgtcatt 420
 gtatcaacag tactattgat ctccagtaca gacatatggt ggaacagaag cctggataca 480
 ggactcagac tcttactggt tggatatccat acgtgatcgt ttgattcagt tcatctctaa 540
 attgcagttt gccgtgactg tgcttttgac atcatggaca gagaaaaaac aacgtcgaaa 600
 aacaactgcc actttatgta tactcaacat tgtcttttct ccattcgtgt tggatcatcat 660
 agttttttct acactactct cttctccctt actccctctt ttcacccttc ctgtgttctt 720
 ggtgggggtt ccccgacctt ttcagagttg gccaggagca gcakgcacca cagcctgtgt 780
 gtgtgcagat acagtgtact actaccaaact ggtgccagg ttgactgctg tactgcagac 840
 tgcaatggca gctggaaagt taggtctcct cctacctgga tctcattact tgggccgttt 900
 tcaggatcgt ttaatgtgga taatgattct ggaatgtggc tatacttact gctctattaa 960
 cattaagggg ttagaattgc aggaacatc ctgtcatact gcagaagctc gcagagttga 1020
 tgaagttttt gaagatgctt ttgagcaaga atacacaaga gtatgttccc ttaatgaaca 1080
 ctttggaat gtcttgacac cctgtactgt tttgcctgtg aaattgtatt ctgatgccag 1140
 gaatgttcta tcaggcataa ttgattctca tgaaaactta aaagaattta aaggtgacct 1200

| | | | | | | |
|-------------|-------------|-------------|-------------|--------------|-------------|------|
| cattaaagta | cttgtgtgga | tacttgttca | atactgctcc | aaaaggcctg | gcatgaaaga | 1260 |
| gaatgttcac | aacactgaaa | ataaagggaa | agcacctcta | atgttgccctg | ctttgaacac | 1320 |
| tttgccacct | cccaaattccc | cagaagacat | agacagttta | aattcagaaa | cttttaataga | 1380 |
| ctgggtctgat | gataatatatt | ttgatgatga | gccaaactatc | aaaaaagtaa | tagaagaaaa | 1440 |
| acatcagttg | aaagattttgc | caggtacaaa | tttgtttatt | ccaggatcag | tagaatcaca | 1500 |
| gagggttggg | gatcattcta | caggcactgt | tcctgaaaac | gatctttaca | aagcagttct | 1560 |
| attaggatac | cctgctgttg | acaaaggaaa | acaagaggac | atgccatata | ttcctctcat | 1620 |
| ggagttcagt | tgttcacatt | ctcacttagt | atgcttacct | gcagagtggg | ggactagctg | 1680 |
| tatgcccagt | tccaaaatga | aggagatgag | ctcgttattt | ccagaagact | ggtaccaatt | 1740 |
| tggttctaagg | cagttggaat | gttatcattc | agaagagaag | gcctcaaattg | tactggaaga | 1800 |
| aattgccaag | gacaaagttt | taaaagactt | ttatgttcat | acagtaatga | cttgtttatt | 1860 |
| tagttttatt | ggaatagaca | atatggctcc | tagtctctgt | catatatattga | gagtttacgg | 1920 |
| tggtgttttg | ccttggtctg | ttgcttttga | ctggctcaca | gaaaagccag | aactgtttca | 1980 |
| actagcactg | aaagcattca | ggtatactct | gaaactaatg | attgataaag | caagtttagg | 2040 |
| tccaatagaa | gacttttagag | aactgattaa | gtaccttgaa | gaatatgaac | gtgactggta | 2100 |
| cattgggttg | gtatctgatg | aaaagtggaa | ggaagcaatt | ttacaagaaa | agccatactt | 2160 |
| gttttctctg | gggtatgatt | ctaatatggg | aatttacact | gggagagtgc | ttagccttca | 2220 |
| agaattattc | atccaagttg | gaaagttaaa | tcctgaagct | gttagaggtc | agtgggccaa | 2280 |
| tctttcatgg | gaattacttt | atgccacaaa | cgatgatgaa | gaacgttata | gtatacaagc | 2340 |
| tcattccacta | cttttaagaa | atcttacggg | acaagcagca | gaacctcccc | tgggatatacc | 2400 |
| gattttattct | tcaaaacctc | tccacataca | tttgtattag | agctcatttt | gactgtaattg | 2460 |
| tcattcaaatg | caatgttttt | attttttcat | cctaaaaaag | taactgtgat | tcttgtaact | 2520 |
| tgaggacttc | tccacacccc | cattcagattg | cctgagaaca | gctaagctcc | gtaaaagttgg | 2580 |
| ttctcttagc | cactttaattg | gttctaaaaa | acagcaaaaa | catctttatg | tctaagataa | 2640 |
| aagaactatt | tggccaatat | ttgtgccctc | tggacttttag | taggcttttg | taaatgtgag | 2700 |
| aaaacttttg | tagaattatc | atataatgaa | ttttgtaattg | ctttcttaaa | tgtgttatag | 2760 |
| gtgaattgcc | atacaaagtt | aacagctatg | taattttttac | atacttaaga | gataaacata | 2820 |
| tcagtgttct | aagtagtgat | aatggatcct | gttgaagggt | aacataatgt | gtatatattt | 2880 |
| gtttgaaata | taatttatag | tatttttcaa | tgtgctgatt | tattttgaca | tctaatatct | 2940 |
| gaatgttttt | gtatcaagta | gtttgttttc | atagacttca | attcataaac | tttaaaaaac | 3000 |
| ttttaataaaa | atatttttct | tcctttttcaa | atatacttct | aataatagt | aaaggagcgg | 3060 |
| ggttcaccca | ttcatcatgt | gaatattcac | aggaagagca | atgttagggg | aatatgcgta | 3120 |
| tgactactaa | agcatatatc | tgactcatta | tgtatcgctt | tcaagtgaat | ttactgcttc | 3180 |
| tgaaaaatga | tttaccacac | aggactacca | gttactagt | tcttaaggta | tatgaactaa | 3240 |
| agtcagaagg | agatggaaga | aaatttttat | aatacgatct | gaattttatt | ttcattctct | 3300 |
| tcttgcttag | gaacgtttta | cagatacatg | taagggg | | | 3337 |

<210> 166

<211> 510

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (503)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (504)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (508)

<223> n equals a,t,g, or c

<400> 166

| | | | | | | |
|-------------|------------|------------|-------------|------------|------------|-----|
| gattatatta | gtcttggtct | ttttagaac | tagtttgctt | catcactttg | ctggcttctc | 60 |
| acagattttct | aaaagcaatt | cccaggctat | tgtgggctat | ggtttgatga | tattacttat | 120 |
| aatactgtgg | atacttagag | aaattcaaag | catatatatc | attggaattt | tccgaaatcc | 180 |
| cttttatccg | aaggatgtgc | aaactgtgac | tgtattcttt | gagaagcaaa | ctaggctcay | 240 |
| gaagattggg | attgtcagac | ggattttgct | aacttttagta | tcaccttttg | ccatgatagc | 300 |
| atttctttca | ttggacagtt | ccttacaagg | gctccactca | gtgtctgtct | gtattggatt | 360 |
| cacaagagcc | tttagaattg | tatggcagaa | tacagaaaat | gctttattgg | agacagtcac | 420 |
| tgtatcaaca | gtacacttga | tctccagtac | agacatatgg | tggaacagaa | gcctggatac | 480 |

agggggaacc cacttcgtga acnncgtntc

510

<210> 167
 <211> 1367
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (1339)
 <223> n equals a,t,g, or c

<400> 167
 gggcggtctc gcggggccgg gcgaggagtc cagagagcca tggccgcctt gcgtgtcctg 60
 ctgtcctgcg cccgcggccc gctgaggccc ccggttcgct gtcccgcctg gcgtcccttc 120
 gcctcggttg ctaactttga gtacatcatc gcagaaaaaa gaggggaagaa taacaccgtg 180
 ggggttgatcc aactgaaccg ccccaaggcc ctcaatgcac ttgcatgg cctgattgac 240
 gagctcaacc aggccctgaa gatcttcgag gaggaccggg ccgtgggggc cattgtcctc 300
 accggcgggg ataaggcctt tgcagctgga gctgatatca aggaaatgca gaacctgagt 360
 ttccaggact gttactccag caagtctctt aagcactggg accacctcac ccaggtaag 420
 aagccagtca tcgctgctgt caatggctat gcctttggcg ggggctgtga gcttgccatg 480
 atgtgtgata tcatctatgc cggtgagaag gccagtttg cacagccgga gatcttaata 540
 ggaaccatcc caggtgcggg cggcaccag agactaccc gtgctgttgg gaagtcgctg 600
 gcgatggaga tggtcctcac cggtgaccgg atctcagccc aggacgcaa gcaagcaggt 660
 cttgtcagca agatttgtcc tgttgagaca ctggtggaag aagccatcca gtgtgcagaa 720
 aaaattgccg gcaattctaa aattgtagta gcgatggcca aagaatcagt gaatgcagct 780
 tttgaaatga cattaacaga aggaagtaag ttggagaaga aactctttta ttcaaccttt 840
 gccactgatg accggaagaa agggatgacc gcgtttgtgg aaaagagaaa ggccaacttc 900
 aaagaccagt gagaaccagc tgcccctgct tcacacctct gcttggagag gacaagtgca 960
 gcctgtcagt tttagaagca agtaaatcat cctcttttca agagcagtgt ccgtggtgtg 1020
 cagttcctct ccaattgctg cgtggtcgtg gcccgacctc tcacggcatg acagccttcg 1080
 tcaccagacc tgtgagggtc ctgactggag caccttctaa atctaagatt ctgctgagga 1140
 gccccgcgtg gtccctctgg gcattgctgt ctcgacgga aagcggggcc tgtgggtcct 1200
 tgtgtccctg ccgctgaaga atggggctgc tctgagggaa acgctgtctc ttcatacaga 1260
 tgctgattaa agtgatagcg attcagatta aaaaaaaaaa aaaaaaaag ggattcgaaa 1320
 tccaatttat ggatacctng accccaaggg gggcccgtaa cccattc 1367

<210> 168
 <211> 594
 <212> DNA
 <213> Homo sapiens

<400> 168
 gggaggaaaa tggcggtcgc tggagccgcc gaccaagagg cttgggagtc tgtacctttc 60
 ccgaccgggc cactggaagt tggagcctcc gccgagtcgc agacaacgcc tccgggaggg 120
 ccttcctgat gcgcttgctt gctccctggt ctctctgcat ggggaaggag tgttcccagc 180
 ttgcaaactc cagctttgccc tgtgagagga acaagcgtcc ctgatccaga aggtgttcgg 240
 atggagatgg cgagttctgc tggctcctgg ctctctggct gcctcatccc tctcgtcttc 300
 ctccggctgt ctgtgcatgt gtcaggccac gcaggggatg ccggcaagtt ccacgtggcc 360
 ctactagggg gcacagccga gctgctctgc cctctctccc tctggcccgg gacggtacct 420
 aaggakgtga ggtggctgcg gtccccattc ccgcagcgtt cccaggctgt tcacatattc 480
 cgggatggga aggaccagga tgaagatctg atgccggaat ataaggggag gacggtgcta 540
 gtgagagatg cccaagaggg aagtgtcact ctgcagatcc ttgacgtgcg cctt 594

<210> 169
 <211> 684
 <212> DNA
 <213> Homo sapiens

<400> 169
 cggacgcgtg ggtcgcccac gcgtccgtgt ttccattagt gatactgatg tctcactggt 60
 gttctctccg agttgacttt tctgtgcctt tgtgcatgct cttatctcct ctgcttgga 120
 tgtccttttc agcctgtcaa actccttcaa aatccagctc agatgttaca ttttctttta 180
 gcaactcctga cccaccccc caaatagact tagtccagcc ttcttctggg ttcccacagc 240
 actcagtaca gtttgaaagg tcctttataa yagtcattat tacatttttc aaaaataatt 300
 tcatattcat taacctcatt agattataag cacctcaatt atgtagactg ttttatcact 360

| | | | | | | |
|------------|------------|------------|-------------|------------|------------|-----|
| gctgwcccg | cacagcacct | ggcacagtta | gctgttcaag | acatctctgt | tgagtgggta | 420 |
| aatgaatgag | ttccactcca | ggttcctgtg | tttgkgacct | ccaggggcct | cttctcttcc | 480 |
| cttccccctt | tcacgtaggc | tgatgccctg | gtcttccagc | tatgcactct | acctgcctct | 540 |
| cgawgctcta | agccgatgtg | tccatcattt | ggctgtttgc | atattctgat | tcatgacatt | 600 |
| ctcctgcaca | gtgctggctg | acactctgta | gcccatacata | tctgacttct | ctggccagcc | 660 |
| tgtatgccta | ccatcagctc | gccc | | | | 684 |

<210> 170
 <211> 1494
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (345)
 <223> n equals a,t,g, or c

| | | | | | | |
|------------|-------------|------------|-------------|------------|-------------|------|
| <400> 170 | | | | | | |
| gaattcttcc | tggaacttgat | ccttcccttc | aggttccttc | tggeccaggg | tgtgtctaaa | 60 |
| aatatcacc | gggagttaga | gcctagaatg | gggacctcac | gactctgcct | gatgccttat | 120 |
| tcaactgtgg | ctgagatggg | atztatgttg | caaaacaaag | tcctgtttat | cctttcctct | 180 |
| cctcttctca | aggagaagga | tggaatctct | tttgagctg | ggagccttcc | tgctttgat | 240 |
| tgggggagtg | gtgacacaag | cgctccctta | gccgcattgg | ctggtgtctc | actaggctcat | 300 |
| gtacctccaa | gtccactggc | tctgagccca | gccagcact | acaanttgcc | taggagttac | 360 |
| agtccttgtg | amctagcctg | ccttttactg | ttattttagga | ccccagagca | cttttagcctg | 420 |
| tggtggcgag | gcttgcagaa | actccagttc | caacctccag | gctgtgtgat | tgtcctgtcc | 480 |
| ctggggctgg | tctaaatgct | ccattcattg | gcattggctg | agttctgccg | ggattggcag | 540 |
| cactgcgttc | cggtctgtag | tcccacagtt | gctgtgctct | ttccccgtgt | gcagcgcaga | 600 |
| ttcttctct | gtgccctgtg | gttgctacga | gcgcattggg | gagggctggg | gtcagcaatt | 660 |
| caagactgtc | tttctatcc | tcttactg | ctcttccagc | aatatgaagg | tactgtgatt | 720 |
| gctcacatga | tttttggttc | ttatgaagg | gctttttgtg | taggtgggtg | tcagatttgg | 780 |
| tgttcctgca | gggaggacaa | tcggtggagg | cttctatttg | gccatattgc | tctgcctccc | 840 |
| attccagctt | gtttctat | ttaatttttg | ttgcaatgga | gtskyytgcc | tgccctgaa | 900 |
| taatatttaa | ataaatcaca | aggacttgaa | actacaaaat | gtatacttag | agccaaagtc | 960 |
| accttacttg | taagaactgg | aaatggggat | aatgctctct | atggttatgc | agcctactct | 1020 |
| tttactaacc | tttctggact | agatctttga | agtgcgtctt | agctttcctc | ccttctgaa | 1080 |
| gagagcagag | atagtgtctg | tttaactgtg | gtcatacatg | tatgaggaat | aacttttagtg | 1140 |
| tgagctgttg | gttttaaaga | gtcatatatt | attctatgca | cttttgtaag | ttcattttat | 1200 |
| aatgagcaga | ttggtcaact | gacatttttg | attatttgta | atacatgtgt | tgcttggaa | 1260 |
| aatactgtta | atctccagaa | atataagtga | accttagctt | ttctgttgg | ggcttttaaa | 1320 |
| ctttttatga | tgggaaaatg | tgtgaatttt | ctcctgggaa | agtatagact | ggagacttag | 1380 |
| ataccagtag | atgaattgag | gaatttctgt | gtagcagttt | aatatagaaa | agagttagct | 1440 |
| gtccatgagg | aagggtctta | agaacaacaa | taactaccaa | aaaaaaaaaa | aaaa | 1494 |

<210> 171
 <211> 610
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (602)
 <223> n equals a,t,g, or c

| | | | | | | |
|------------|-------------|------------|------------|------------|------------|-----|
| <400> 171 | | | | | | |
| gagaggagag | actaaggacg | ctaggtgggc | agggtcttcc | acttgcagcc | tcgaagcgga | 60 |
| ggatccctgt | gtcccagccg | ggcatggccg | acccccacca | gcttttcgat | gacacaagtt | 120 |
| cagcccagag | ccggggctat | ggggcccagc | gggcacctgg | tggectgagt | tatcctgcag | 180 |
| cctctcccac | gccccatgat | gccttctctg | ctgacccggg | gtccaacatg | gccatggcct | 240 |
| atgggagcag | cctggccg | cagggcaagg | agctgggtga | taagaacatc | gaccgcttca | 300 |
| tccccatcac | caagctcaag | tattactttg | ctgtggacac | catgtatgtg | ggcagaaagc | 360 |
| tgggcctgct | gttcttcccc | tacctacacc | aggactggga | agtgcagtac | caacaggaca | 420 |
| ccccgggtgg | ccccgcgttt | gacgtcaatg | ccccggacct | ctacattcca | gcaatggctt | 480 |
| tcatcaccta | cgttttgggtg | gctggcttgc | gctggggacc | caggataggt | tytccccagm | 540 |
| cctcctgggg | ctgcaagcga | gctcagccct | ggctgctgac | cctgaagtgc | tggcatctgc | 600 |
| tnagcttatt | | | | | | 610 |

<210> 172
 <211> 654
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (594)
 <223> n equals a,t,g, or c

| | |
|--|-----|
| <400> 172 | |
| aaggcattca tttcctccta cgggtggatgc ggacgccggg aggaggagag cccagagag | 60 |
| aggagctggg agcggaggcg cagagaacac gtagcgactc cgaagatcag cccaatgaa | 120 |
| catgtcagtg ttgactttac aagaatatga attcgaaaag cagttcaacg agaatgaagc | 180 |
| catccaatgg atgcaggaaa actggaagaa atctttcctg ttttctgctc tgtatgctgc | 240 |
| ctttatattc ggtggtcggc acctaatagaa taaacgagca aagtttgaac tgaggaagcc | 300 |
| attagtgtctc tggctctctga cccttgcaagt cttcagtata ttcggtgctc ttcgaactgg | 360 |
| tgcttatatg gtgtacattt tgatgaccaa aggcctgaag cagtcagttt gtgaccagkg | 420 |
| tttttacaat ggacctgtca gcaaattctg ggcttatgca tttgtgctaa gcaaagcacc | 480 |
| cgaactagga gatacaatat tcattattct gaggaagcag aagctgatct tcctgcactg | 540 |
| gtatcaccac atcactgtgc tcctgtactc ttggtactcc taaaaagaca tggnttgccg | 600 |
| gggagggttg ttcatgacta tgaactatgg cgtgcacgcc gtgatgtact cttta | 654 |

<210> 173
 <211> 2046
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (33)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (96)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (100)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (113)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (122)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (131)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (1986)
 <223> n equals a,t,g, or c

<220>
 <221> SITE

<222> (1993)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (2019)

<223> n equals a,t,g, or c

<400> 173

| | | | | | | |
|-------------|-------------|-------------|-------------|-------------|-------------|------|
| cctgggtattc | aggactgaat | tgggaagtctg | agnatcagtg | tggagccata | tctcggctgg | 60 |
| caaagccgga | ttgtccgtct | gattatctca | atgtcnagtn | cccacctgct | cgntgtgatc | 120 |
| ancactaaca | nggaacaaat | tcaaggacaa | cctgtytttg | agccaggcag | cctcagacac | 180 |
| ctgcctgtgg | ccccckctcc | acttctcctg | cccggtatgcc | agtgtctccga | gctcagacag | 240 |
| aggaagccct | gcagaaagtt | ccatcaggct | gtttcctaaa | ggatgtgtga | acgggagatg | 300 |
| atgcactgtg | ttttgaaagt | tgtcatttta | aagcatttta | gcacagttca | tagtccacag | 360 |
| ttgatgcagc | atcctgagat | tttaaatacct | gaagtgtggg | tggcgcacac | accaagtagg | 420 |
| gagctagtca | ggcagtttgc | ttaaggaact | tttgttctct | gtctcttttc | cttaaaattg | 480 |
| ggggtaagga | gggaaggaaag | agggaaagag | atgactaact | aaaatcattt | ttacagcaaa | 540 |
| aactgctcaa | agccatttaa | attatatacct | catttttaaaa | gtkacatttg | caaataatttc | 600 |
| tccctatgat | aatgtagtcg | atagtgtgca | ctctttctct | ctctctctct | ctctcacaca | 660 |
| cacacacaca | cacacacaca | cacacacaca | sacacggcac | cattctgcct | ggggcactgg | 720 |
| aacacattcc | tgggggtcac | cgatgggtcag | agtcactagr | agttacctga | gtatctctgg | 780 |
| gaggcctcat | gtctcctgtg | ggctttttac | caccactgtg | caggagaaca | gacagaggaa | 840 |
| atgtgtctcc | ctccaaggcc | ccaaagcctc | agagaarggg | tgtttctggg | tttgccttag | 900 |
| caatgcacgc | gtctctgagg | tgacactctg | gagcgggtga | agggccacaa | ggtgcagggt | 960 |
| taatactctt | gccagttttg | aaatatagat | gctatgggtc | agattgtttt | taatagaaaa | 1020 |
| ctaaaggggc | aggggaagtg | aaaggaaaga | tggaggtttt | gtgcggctcg | atggggcatt | 1080 |
| tggaaacttct | ttttaaaagtc | atctcatggg | ctccagtttt | cagttggaac | tctggtgttt | 1140 |
| aacacttaag | ggagacaaag | gctgtgtcca | tttggcaaaa | cttccttggc | cacgagactc | 1200 |
| taggtgatgt | gtgaagctgt | gcagtctgtg | gtgtggagag | cagccatctg | tctggccatt | 1260 |
| cagaggattc | taaagacatg | gctggatgcg | ctgctgacca | acatcagcac | ttaaataaat | 1320 |
| gcaaagtcaa | catttctccc | tctgggcctt | gaaaatcctt | gcccttatca | tttgggggtga | 1380 |
| aggagacatt | tctgtccttg | gcttcccaca | gcccacaacg | agtctgtgta | tgattcctgg | 1440 |
| gatccaacga | gccctcctat | tttcacagtg | ttctgattgc | tctcacaycc | caggcccattc | 1500 |
| gtctgttctc | tgaatgcagc | cctgttctca | acaacaggga | ggatcatggaa | cccctctgtg | 1560 |
| gaaccacaaa | ggggagaaaat | gggtgataaa | gaatccagtt | cctcaaaaacc | ttccctggga | 1620 |
| ggctgggtcc | ctctcctgct | gggtgggtgct | ttctcttgca | caccactccc | accacggggg | 1680 |
| gagagccagc | aacccaacca | gacagctcag | gttgtgcac | tgatggaaac | cactgggctc | 1740 |
| aaacacgtgc | tttattctcc | tgtttatttt | tgctgttact | ttgaagcatg | gaaattcttg | 1800 |
| tttgggggat | cttgggggcta | cagtagtggg | taaacaaatg | cccaccggcc | aagaggccat | 1860 |
| taacaaatcg | tccttgtcct | gaggggcccc | agcttgctcg | ggcgtggcac | agtggggaaa | 1920 |
| tccaagggtc | acagtatggg | rgaragggtg | caccctgcca | ccctgctaac | tttcctccgc | 1980 |
| ttaaanacag | tgnttttctt | gccccagggt | taaacctgnt | ttcccaccaa | gcaaaaaaca | 2040 |
| agccca | | | | | | 2046 |

<210> 174

<211> 1439

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (37)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (61)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (73)

<223> n equals a,t,g, or c

<400> 174

| | | | | | | |
|-------------|-------------|-------------|-------------|-------------|-------------|------|
| cctaaacgtc | caacgtcaat | gccccaaaacc | accagangcc | aacacaccta | cgtgtaaaca | 60 |
| nctacgacgt | tangtttggg | gtaaatgtgg | ggaatgaaac | tgccatgaag | gcccctgaat | 120 |
| taaaggatgt | ggggaagtgg | gctgcggtcc | actgtccggc | cttgcaaggc | cmccyggagg | 180 |
| cctgtctgtt | agccagtggt | ggaggagcaa | ggcttcagga | agggccagcc | acatgccatc | 240 |
| ttccctgcga | tcaggcaaaa | aagtggaatt | aaaaagtcaa | acctttatat | gcatgtgtta | 300 |
| tgtccatttt | gcaggatgaa | ctgagtttaa | aagaattttt | ttttctcttc | aagttgcttt | 360 |
| gtcttttcca | tcctcatcac | aagcccttgt | ttgagtgtct | tatccctgag | caatctttcg | 420 |
| atggatggag | atgatcatta | ggtacttttg | tttcaacctt | tattcctgta | aatattttctg | 480 |
| tgaaaactag | gagaacagag | atgagatttg | acaaaaaaaa | attgaattaa | aaataacaca | 540 |
| gtcttttttaa | aactaacata | ggaaagcctt | tcctattatt | tctcttctta | gcttctccat | 600 |
| tgtctaaatc | aggaacacag | gaaaacacag | ctttctagca | gctgcaaaat | ggtttaatgc | 660 |
| cccctacata | tttccatcac | cttgaacaat | agcttttagct | tgggaatctg | agatatgatc | 720 |
| ccagaaaaca | tctgtctcta | cttcggctgc | aaaacccatg | gtttaaatct | atatggtttg | 780 |
| tgcattttct | caactaaaaa | tagagatgat | aatccgaatt | ctccatata | tcactaatca | 840 |
| aagacactat | tttcatacta | gattcctgag | acaaatactc | actgaagggc | ttgtttaaaa | 900 |
| ataaattgtg | ttttggctctg | ttctttagta | taatgccctt | ctatttttagg | tagaagctct | 960 |
| ggaatccctt | tattgtgctg | ttgctcttat | ctgcaagggtg | gcaagcagtt | cttttcagca | 1020 |
| gattttggcc | actattcctc | tgagctgaag | ttctttgcat | agatttggct | taagcttgaa | 1080 |
| ttagatccct | gcaaaggcct | gctctgtgat | gtcagatgta | attgtaaatg | tcagtaatca | 1140 |
| cttcatgaac | gctaaatgag | aatgtaagta | tttttaaatg | tgtgtatttc | aaatttgttt | 1200 |
| gactaattct | ggaattacaa | gatttctatg | caggattttac | cttcatcctg | tgcatgtttc | 1260 |
| ccaaactgtg | aggagggaag | gctcagagat | cgagcttctc | ctctgagttc | taacaaaatg | 1320 |
| gtgctttgag | ggtcagcctt | taggaagggtg | cagctttgtt | gtcctttgag | ctttctgtta | 1380 |
| tgtgcctatc | ctaataaaact | cttaaacaca | aaaaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | 1439 |

<210> 175

<211> 675

<212> DNA

<213> Homo sapiens

<400> 175

| | | | | | | |
|-------------|------------|------------|------------|-------------|------------|-----|
| gattagatgg | cgctagatat | ttcacttttt | tatttgkttt | atTTTTTTTT | TTTTTTgaga | 60 |
| tggaattttct | ctcttattgc | ccaggctgga | gtgcagtggc | acgatcttgg | ctcacctcaa | 120 |
| cctccgcctc | ccgggttgaa | gcgattctcc | ttcctcggcc | tcccagacag | ctgggattac | 180 |
| aggcatgcgc | caccatgccc | ggctaatttt | gtatttttag | tagagatggg | gtttctccat | 240 |
| gttggtcagg | ctggcttga | actccctacc | tcaggtggtc | cacctgcctg | ggcctcccaa | 300 |
| agtgtcggga | ttacaggcgt | cagccaccgt | gcctggcctg | agaattcaca | tttttaacaa | 360 |
| tttcccaggg | gatgttagtg | cagcctgtct | ggggaccatg | gttcgagaac | catagctcta | 420 |
| gatttttcta | agagcatttc | tgtctccatg | ccagacctgt | tttctctccat | gaagtatact | 480 |
| atttcaatgc | tcgacttagt | gtttatgttt | tactctttct | actgttttta | caatcttaat | 540 |
| ccagcctata | aattcctctg | ggcagaaatt | ataccttcca | cactctttca | ttttctgttt | 600 |
| tggaataata | tgagtacatc | ttcagcatga | ttaataatag | aatggagaaa | ggggaaaacc | 660 |
| tcgactatc | aacc | | | | | 675 |

<210> 176

<211> 8446

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (2333)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (3087)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (4356)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (6401)

<223> n equals a,t,g, or c

<400> 176

| | | | | | | |
|-------------|-------------|-------------|-------------|-------------|-------------|------|
| agatttggttt | cgtttcgccg | actgctgaat | ttaccccgaa | aaccgctcga | acgccggatc | 60 |
| tgcgtagcga | cctcgcttat | cgccctgcgta | ttgtggtgac | cgacgccgat | gatgcgttac | 120 |
| gccagggaat | gccagtgcg | gtacaattcg | gtgacgaggc | aggacatgaa | tgatgccgtt | 180 |
| atcacgctga | acggcctgga | aaaacgcttt | ccgggcatgg | acaagcccgc | cgtcgcgccg | 240 |
| ctcgattgta | ccattcacgc | cggttatgtg | acgggggttg | tggggccgga | cgggtgcagg | 300 |
| aaaaccacgc | tgatgcggat | gttggcgagg | ttactgaaac | ccgacagcgg | cagtgccacg | 360 |
| gtgattggct | ttgatccgat | caaaaacgac | ggcgcgctgc | acgccgtgct | cggttatatg | 420 |
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| ggcgaaggga | tgtaaatcct | ctggagtacc | tcgtatctcg | acgaagccga | gcagtgcctg | 780 |
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| caaaccatgg | ccggacgcag | ctttctgatg | accagtccac | acgagggcaa | ccgcaaaact | 900 |
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| | | | | | | |
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| gccactacca | gtaaatgcaa | cataatctgc | cagcaactta | gacccgttgc | gacacgaaca | 4500 |
| cgttgttgcc | acttcatggc | ttctctcctg | aagaatttat | ctctacttac | tcagagtacc | 4560 |
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| gatatgattc | cattctttta | gttttcctta | gaaaaaatat | taatattcac | caycaataaw | 8400 |
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<211> 730

<212> DNA

<213> Homo sapiens

<400> 177

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| ctcgaggccc | cacaatgggc | gctggattgg | atgtttggca | actgattccg | actggatggg | 120 |
| gagctgggga | gactgtggga | tgggatggca | gctccggggc | ctgtcagctg | tgggacctgtg | 180 |
| gttcacagct | ggggactccc | acctttctgt | ccaggctctgt | ggagggggcc | cagccctcac | 240 |
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<210> 178

<211> 621

<212> DNA

<213> Homo sapiens

<400> 178

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| actttaggca | tgctctgcca | cgctgggcta | ttattgatgt | atttattttt | agagatgagg | 120 |
| tctcactgtg | ttgcccagac | tgggtctgaa | ctcttggcct | caagccatcc | tcctttctca | 180 |
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| ggcgtgagc | ttgggtgcatg | aaacccctaa | catttatttag | gcattgtgga | aagtacttcc | 360 |
| cgtgtattgt | ctcagaaaaca | acacagtgtc | ccgacaaaaa | cttgagagtc | aagtggccca | 420 |
| cagcgggcaa | gttgcttatt | ttctcttagg | tttctcatct | gtaaagtggg | aataatatta | 480 |
| gtacccccct | gtaggatgat | tataatgtct | tgtggctaca | agccaaggaa | tgccagggaat | 540 |
| tcctggaagc | caatagatgt | cctatccctg | ctcggaagct | agaagaggca | agaaagaatt | 600 |
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<211> 558

<212> DNA

<213> Homo sapiens

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<222> (133)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (395)

<223> n equals a,t,g, or c

<220>
 <221> SITE
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<220>
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 <222> (409)
 <223> n equals a,t,g, or c

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 gaacacactc aggtccagggt ttcttttctc ctggaatacc tatcctcttt gtccaggctt 480
 ctgcagtcac gtttatttgt ggagcctgac cttgtgattc aggatgagct tgtgaaacct 540
 cttatcacca atatcattgg aattctcacc atatgtacca aagatgtatt agataaagag 600
 ttaatatcag ctttttatca cacatggaca catttattta atcttctggc catgctcctg 660
 aggaaagctg gtgccatcac actcccgtgt gttaccgtgg ccctggcaag cactggacag 720
 cggcgattga tatgttctgc acatgtgcrs gcttgtctgc cacgtgtcct gccctgtwta 780
 ctgccagctt gcaattcctt tctgttctct tgaccgaaga agcaaaaggg catctycagg 840
 ctaagagcaa aacacatttw tgctgtagtc caacagtggc ttcacttctt gatgactctc 900
 aggaaaatca gaaatctcta gaacaactta gtgatgtaat ccttcagtgc tatgaaggga 960
 aatcctccaa agatatcctg aaaagagtag ctgcaaatgc attgatgtca ctgctggctg 1020
 tcagtagaag agcacagaaa catgctttga aagccaatct tatagacaat tgcattggagc 1080
 agatgaaaca cataaatgca caactgaacc tagattctct gaggcctggg aaagcagcat 1140
 traaaaaaaa ggaggatggt gttatttaaag agttaagcat tgccatgcag ctccctaagaa 1200
 actgtsttta tcaaaatgag gaatgtaaag aagcagctct tgaagctcac cttgtccctg 1260
 tcttgcatc tctctggcct tggattttga tggatgatc attgatgcaa atttctctgc 1320
 agctcctttg tgtctatact gcaaattttc cmaatgggtg cagttctctt tgttgggtcaa 1380
 gttgtggaca acacckggt caagctacac atagaggagc cgtgagcaac tctctggatg 1440
 ctgtgtgatc ctaaaagtgt ggtttcccag atgccactgg nggaacacca cggtttcagc 1500
 agatgggttt ttn 1513

<210> 181
 <211> 777
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (35)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (155)
 <223> n equals a,t,g, or c

<400> 181
 gcaacaaatg attctgaggc ttgatggctg tctanactta ctaacagaga tgagcaaata 60
 caagcacaag agcagccctt tattgcctct tcttatcttt cataatggtt gcttcagtcc 120
 tgcaataaaa cccaagatcc tggctaataa aaaangtcat tactgtgctt gctgcctgtc 180
 tggaaagtga gaatcaaaat gctcagagga ttggagcagc tgcccttttg gctctgattt 240
 acaattatca gaaggcaaaa acagcttttg aaagcccatc agtaaaaaga agagtggatg 300
 aagcatactc cttagcaaaag aaaactttcc caaactcaga agcaaaccct ctaaatgcct 360
 attatttgaa atgtcttgaa aacctcgtgc agctccttaa ttcttcctga gtgccatggg 420
 atgctacacc ttgaagctga cagtcaccaa caggggagct aaagttgaag ccagctgtgt 480
 gtagcagctg ttacctgaag acgtgctacc tctctacaaa gtgttgatcc ctttctttcc 540
 catgagagag agaactgggtg atactccaac accgtccagt tgtggcagct ctccagaagt 600
 aatagcagct gacaactttc tgtgcctttt cctttctgtt gaaaaggcat agaaagtctt 660
 gggaacataa acattttttac cctttttctat gccatttatt ttgtaaaaat cctattttaac 720
 agttatttaa taaaacaata ttttttagaaa ctaaaaaaaa aaaaaaaskg cggccgc 777

<210> 182
 <211> 1909
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (1902)
 <223> n equals a,t,g, or c

<400> 182
 gaaaatatat tagaaaaaaa aaaaaaaca tttgaagcca aatgaacaaa actccagata 60
 ccattgataa gaaattttgc atcaagaagg gcttctgaaa agaccacagt gctccagtcc 120
 cagctccaaa agccactgat gacaagggcc ccactgtgga acctaagtct gggagccccc 180
 tgacttctgg ctggccagag gctgcggctc gtcaagggct tgccctcgctt cagaatcagt 240
 aacatagatc ttaagtgcaa ttgattaata agcagtgaat tactgtagct tccttttagct 300
 ctaccgaact ctttttaaaa actcaaaact gagcagcctt agaaaagggg ttgggggggtg 360
 ggaaccacag gctatttctc taagtgggct gctgtgaagt tttaaatgaa agctctagct 420
 ttaggagctt gagccatttc ctgactgcac tggcctggca gtctggctgc tgcasaagag 480
 ttttttaaga ggggtcsgag cccgcccgtg agagcggkct ttctcaccat gtggggctgt 540
 actacgtggt ggtcttggtt tctcttcaca gaaatgctct ctcaccaact tgccccactg 600
 tcccaactcc tctcctctta gagaaaaaac tgtgattacc tcaacttgaa tatgaaactg 660
 tgattgaaaa aagtcaaaac gtgaagaagg atcaaaagcca aaaaggcaaa actggctgag 720
 gcctctgttg atgtctctca gctactcgg gacgtgaag gggcagctgg cgaaagggca 780
 ttctctggggc cacttgctct gccccactga taaggcacac ccgcggtgca ctgtgagctc 840
 tttgaggact gaggccaggg gatgcctcct ggaacctgcc aggcctctct gttctgtgaa 900
 ggtcagtatc cacttgatcc ctccaggcgg cgctccagggt gggaggagca gggctctctg 960
 ctgtttccaa aggaatggcc atgacactgc ttttgacctt agaagtggat ccaggggacc 1020
 agcaaagagc gggggtgggt tcccagggac aggcagtcct cccggggctt acatgctttt 1080
 tgctaacttt cctattagca gcttcagttt atatcaccca gagtgcgtgg gataatgtt 1140
 aagtcgctga agttacgggt tattttatgt ttttacatgg gatttttctg tttttgattg 1200
 gaagaaggag acagaaattg gaggaatgg gattattatc ctagggaagg gccgttgga 1260
 aggagttgag ccggccctct tgagccctgg gggctatctg acctgaagcc tggacactgg 1320
 gcccttcagg tcgcaagaaa aagttccctc ctaaatctta ttaggatttt ggagaatttt 1380
 tgcacagtaa gaagctctgg gttgctcctt gggcttctca aaagggaataa gttcaattca 1440
 aagattgttaa actacgaagt attccagccg tgttgctgat ctagttggat agttgtacct 1500

| | | | | | | |
|------------|-------------|-------------|-------------|------------|-------------|------|
| caaaaaagta | ggtgagaact | ggcttcctca | ttgtcccagg | atgtcaaata | ctaatagacat | 1560 |
| aagagctcac | ttacgtgccca | aaattcactt | ttatactagt | ttttcagtg | tttaatatatt | 1620 |
| gtaacttaaa | ttttaaaact | cgtattttaca | aacactactg | taacttcagt | gaaactgaat | 1680 |
| tgtgcgattg | aagctttttg | cttatcatag | tattttattac | actacttaat | tcagtaaata | 1740 |
| tataaaagta | gccttcaatt | tatttttata | ttattttaca | tgtttttacc | tgagttgtg | 1800 |
| tatgtgaatt | taccttggtg | atcgagatgt | catgctaagg | accaataaac | tatcactgaa | 1860 |
| caaaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | | 1909 |

<210> 183
 <211> 773
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (47)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (62)
 <223> n equals a,t,g, or c

| | | | | | | |
|------------|------------|------------|------------|------------|-------------|-----|
| <400> 183 | | | | | | |
| actatccacc | agatagatag | ctcactctga | aaatttgagg | ttcattnacc | aatccttttt | 60 |
| tnccttcatt | ccccatatgc | aaattagcag | caatcccaca | attctaaaat | acatcctgaa | 120 |
| atcggaaccc | tctatcacta | ctattaaatc | cacaatttaa | atcaccatca | tctcttatct | 180 |
| ggattctttc | agttacctcc | tgattaatcc | cctgcttctt | gtgttgcttt | ccacagatca | 240 |
| ctgcctgcac | agcaaacaga | atgatttcct | aaaaaaaaaa | aattgagact | gtattgttcc | 300 |
| cttgcttaaa | gccctccaac | agcttcccat | tgcaataaaa | ataaatgtca | ccttcttatt | 360 |
| tggcctataa | ggcctgacgt | ggtttggtc | ctgcctctgt | aaactcatca | tctacccctt | 420 |
| gtccccaggt | tctcatgctc | cagccacagt | ggctaccttc | ctgtcccgcg | aatgtaccca | 480 |
| gtatatacta | cctcagactt | ttgctctgga | acattcgttc | tcatttttgc | atggctaacc | 540 |
| ctttctgaat | tagtcagggt | tctccataga | aagataatca | attggttttt | tatatatttta | 600 |
| aggagatttt | attatggaga | attagcatat | gcaaataatg | agaccacaat | gtgccatcta | 660 |
| caagctggag | acccaagaca | gctgggtggg | taattcartc | tgagtccgaa | ggctgagagc | 720 |
| cagaggaact | gatgggtgtg | atcccagctc | gaaggcaagg | gaagatgaaa | tga | 773 |

<210> 184
 <211> 614
 <212> DNA
 <213> Homo sapiens

| | | | | | | |
|------------|------------|------------|------------|------------|------------|-----|
| <400> 184 | | | | | | |
| gcggcacgag | tgaacatcca | tgtactcacc | atctctttac | cttcttccct | ccctcccctc | 60 |
| cctcctccag | ttgagtctct | ccagaagccc | cggattcaac | aaggggttac | aaagagccat | 120 |
| ggagaagaca | atgaagggtt | ctacaattaa | gattttgctc | tattttttcc | atcatatcta | 180 |
| tgcactctct | cataccttta | tccctctacc | caatccatct | atttttttat | gcattttcaa | 240 |
| gtacattgca | gacattagta | catgacacct | ctaatacagt | ttatgttctt | ttccttttta | 300 |
| ctttatacga | aataaaaatc | acagttaaca | attatcaagt | gcttactgtc | aggcactgtg | 360 |
| ccaagcactt | tccttgcat | acataatttg | aatctcatgg | taaccctata | agtacagtta | 420 |
| ccaccttcat | tttacaatg | agaagaactg | aaacagagaa | caatgggtgc | aattaacatt | 480 |
| ttaaaagtct | ttctatgggc | cattcacagt | gcaagtactt | ttcatgcatt | awctcagtta | 540 |
| atcccttata | gcaatttcat | aaaggcaata | ctattacmga | tgcaaaattg | agactttkag | 600 |
| aaaaagatct | tgga | | | | | 614 |

<210> 185
 <211> 437
 <212> DNA
 <213> Homo sapiens

| | | | | | | |
|------------|------------|------------|------------|------------|------------|-----|
| <400> 185 | | | | | | |
| ctagttctag | atcgcgagcg | ccgccctttt | tttttttttt | tttttttttt | tttttttttt | 60 |
| ttacmtcttt | gkcaaagggt | aaaaaagcat | atatgaaatt | aaaaatagta | tcaaagaatt | 120 |
| caactacaaa | gggcttaaca | aacttcgtaa | attggagata | tataggacat | tgtacctaac | 180 |
| ctaatagaaa | cttaaacatt | ttttagttat | gkatgkcagt | ttttaaccat | gttccataga | 240 |

| | | | | | | |
|------------|------------|------------|------------|-------------|------------|-----|
| ggaatgttaa | caatgtctaa | aaaatcagkg | tcatacaaaa | tacgttattt | cagccaggca | 300 |
| tggcagctca | tgccggtaat | cctagtgtct | tgggaggctg | aggcaggagg | atcacttgaa | 360 |
| gccaggcaag | accatatagk | gagactygtg | ctctgcaaaa | aaaaaaaaaag | ggcggcscce | 420 |
| cttttttttt | tttttta | | | | | 437 |

<210> 186

<211> 587

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (534)

<223> n equals a,t,g, or c

<400> 186

| | | | | | | |
|------------|-------------|------------|------------|------------|-------------|-----|
| gacatccatt | gaagctgcaa | caccaccccc | cgccacttca | cctccttcct | gacatgctct | 60 |
| gctcctcctt | tctccccctc | agcactgctg | ccatctgggc | tgcattattc | tcgggtatgg | 120 |
| gggctgtccg | acattcccca | tcagaaggaa | aaagatccct | gaaaagtagc | aggtgcttac | 180 |
| atttctggcc | tctaccacc | ggctgcagta | gtccccacc | accctgcaat | gtgacaacca | 240 |
| aaaatgtctc | tagatgttgc | cagaagtcct | ctagagatgg | gagggtagca | ctgccacccc | 300 |
| gctgagaatt | cctgctgtca | ctggagtggg | ggctgttttc | tctcccatgc | ctctgggtacc | 360 |
| ttgggggtcc | ccccgtctcc | caagggtctg | ttccaccacc | ctgtccatcc | atcccattg | 420 |
| gctcccagga | ggtttttagct | ccgggcttcc | tgtctccac | accactcctc | acagttctcc | 480 |
| atgatttcaa | catccaggtg | ggcgacgcag | cctctcggtt | ccttgaccct | ctgngtgatc | 540 |
| ctgctgcttc | taccgggcca | accagtactc | ctaggagccc | tcacaat | | 587 |

<210> 187

<211> 1706

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (1424)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1665)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1688)

<223> n equals a,t,g, or c

<400> 187

| | | | | | | |
|-------------|-------------|------------|------------|------------|-------------|------|
| ggcttcctcg | ggtactcggc | cactcggggc | atcgcgggcg | cctttctagc | cgctgtccca | 60 |
| aggggttggtc | tcgcgctttc | ggctgcgagc | tctctgtggt | gctggcagcg | acatgtggcg | 120 |
| cctcccggga | ctcctgggccc | gagctcttcc | ccgtacactg | ggacctagcc | tctggagggg | 180 |
| gactcctaag | tccaccagcc | cagatggggc | tcagactacc | tcctccactt | tgctgggttc | 240 |
| tgtgcctaac | ctcgacaggt | caggtcccca | tggcccagcg | acgagcgggg | gtccaaggctc | 300 |
| ccatggatgg | aaggatgcct | tccaatggat | gtcttcccg | gtctcccga | acaccctatg | 360 |
| ggatgccata | tcttggggca | ctctggccgt | gctggccctg | cagctggcaa | ggcagatcca | 420 |
| cttccaggca | tccctgccag | caggacctca | gcgggtagaa | cactgctcct | ggcacagtcc | 480 |
| cctggaccgt | ttcttctcat | ctcccttgtg | gcacccatgc | tcctcactgc | gacaacacat | 540 |
| cctccccagc | cccgatggcc | cagctcccag | gcacactggc | ctcaggggaa | ccaggcttgg | 600 |
| ccaggaagaa | gcctcagctc | agccccggaa | cttctcacac | aactctttga | gaggagctcg | 660 |
| tcctcaggac | ccctctgagg | aaggtcccgg | tgattttggc | ttcctgcatg | ccagtagtag | 720 |
| catcgagtcc | gaggcaaaac | cagcccagcc | tcagcccact | ggtgaaaagg | aacaagataa | 780 |
| atcaaaaact | ctttcccttg | aggaggctgt | gacttccatt | cagcagctct | tccagctcag | 840 |
| tgtttccatc | gctttcaact | tcctgggaac | agagaacatg | aagagtggcg | accacacggc | 900 |
| agccttttct | tacttccaga | aagctgcagc | ccgcgggtac | agcaaagcgc | agtacaatgc | 960 |
| gggcttgtgt | catgagcatg | gcagaggcac | ccccagggac | attagcaagg | cggtccttta | 1020 |
| ttatcagttg | gctgccagcc | agggccacag | cctggctcag | taccgctatg | ccagggtgct | 1080 |

| | | | | | | |
|------------|-------------|------------|------------|-------------|------------|------|
| actacgagac | ccagcctctt | cgtggaaccc | tgagcggcag | agggcagtgt | ccttgctgaa | 1140 |
| gcaggctgca | gactcaggct | tgagagaggg | ccaagctttc | ctcgggggtgc | ttttcaccaa | 1200 |
| ggagccctac | ctggatgagc | agagagctgt | gaaatatctt | tggcttgagc | ccaacaatgg | 1260 |
| ggactcacag | agcagggtacc | accttggaat | ttgctatgag | aaaggccttg | gtgtgcagag | 1320 |
| gaatctggga | gaggccttga | gatgttacca | gcagtcagcc | gctctgggaa | atgaggccgc | 1380 |
| ccaggagagg | ctgcgagccc | tcttttccat | gggggctgca | gccngggggc | ccagcgacct | 1440 |
| gacagttaca | ggactgaagt | ctttctccag | cccctccctc | tgcagcttga | acaccctgct | 1500 |
| agcaggaacc | tcacgcctac | cacatgcctc | gagcacaggc | aaccttgggc | tcctctgcag | 1560 |
| aagtgggcat | ytcgagacca | gcctggaagc | ctccagcagg | gctattcccc | cacamccyta | 1620 |
| cccaytgga | aggagtgttk | taagaytagg | ttttggytaa | ggaanttcca | gcggggggtt | 1680 |
| caagtttncc | caaggcaatt | ttcaag | | | | 1706 |

<210> 188

<211> 1150

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (407)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (413)

<223> n equals a,t,g, or c

<400> 188

| | | | | | | |
|------------|------------|-------------|------------|-------------|------------|------|
| ggtcgaccca | cgcgctccga | ctcagacacc | gtgtcctctt | gcctgggaga | ggggaagcag | 60 |
| atctgaggac | atctctgtgc | caggccagaa | accgccacc | tgagttcct | tctccgggat | 120 |
| ggacgtgggg | cccagctccc | tgccccacct | tgggctgaag | ctgctgctgc | tctgctgct | 180 |
| gctgccccct | aggggccaag | ccaacacagg | ctgctacggg | atcccaggga | tgcccggcct | 240 |
| gccccggggc | ccagggaagg | atgggtacga | cggactgccg | gggcccaagg | gggagccagg | 300 |
| aatcccagcc | attcccggga | tccgaggacc | caaagggcag | aaggggagaac | ccggcttacc | 360 |
| cggccatcct | gggaaaaaat | gccccatggg | accccttggg | atgccanggg | tgncggggcc | 420 |
| catgggcakm | cctggaragc | cagaaaattcc | agtcagtgtt | cacggtcact | cggcagacct | 480 |
| accagcccc | tgcacccaac | agcctgatca | gattcaacgc | ggtcctcacc | aaccgcaggg | 540 |
| gagattatga | cacgagcact | ggcaagttca | cctgcaaagt | ccccggcctc | tactactttg | 600 |
| tctaccacgc | gtcgcataca | gccaacctgt | gcgtgctgct | gtaccgcagc | ggcgtcaaag | 660 |
| tggtcacctt | ctgtggccac | acgtccaaaa | ccaatcaggt | caactcgggc | ggtgtgctgc | 720 |
| tgaggttgca | ggtgggagag | gaggtgtggc | tggctgtcaa | tgactactac | gacatggtgg | 780 |
| gcatccaggg | ctctgacagc | gtcttctccg | gcttctgct | cttccccgac | tagggcgggc | 840 |
| agatgcgctc | gagaccacag | ggccttccac | ctccctcagc | ttcctgcatg | gaccacctt | 900 |
| actggccagt | ctgcatacct | gcctagacca | ttctccccct | caggagagccc | acctgaccc | 960 |
| acccccactg | cacccccctc | ccatgggttc | tctccttctt | ctgaacttct | ttaggagtca | 1020 |
| ctgcttgtgt | ggttctctgg | acacttaacc | aatgccttct | ggtactgcca | ttcttttttt | 1080 |
| tttttttcaa | gtattggaag | gggtggggag | atatataaat | aaatcatgaa | atcaawaaaa | 1140 |
| aaaaaaaaag | | | | | | 1150 |

<210> 189

<211> 1233

<212> DNA

<213> Homo sapiens

<400> 189

| | | | | | | |
|------------|------------|------------|------------|------------|------------|-----|
| gcgagcggcc | gctcgcggat | ctagaactag | tccgacgcgt | gggaagcaga | tctgaggaca | 60 |
| tctctgtgcc | aggccagaaa | ccgccacact | gcagttcctt | ctccgggatg | gacgtggggc | 120 |
| ccagctccct | gccccacctt | gggctgaagc | tgctgctgct | cctgctgctg | ctgccccca | 180 |
| ggggccaagc | caacacaggg | tgctacggga | tcccagggat | gcccggcctg | cccggggcac | 240 |
| cagggaagga | tgggtacgac | ggactgccgg | ggcccaaggg | ggagccagga | atcccagcca | 300 |
| ttcccgggat | ccgaggaccc | aaagggcaga | agggagaacc | cggcttacct | ggccatcctg | 360 |
| ggaaaaatgg | ccccatggga | ccccctggga | tgccaggggt | gcccggcccc | atgggcatcc | 420 |
| ctggagagcc | aggtgaggag | ggcagataca | agcagaaatt | ccagtcagtg | ttcacggtca | 480 |
| ctcggcagac | ccaccagccc | cctgcaccca | acagcctgat | cagattcaac | gcggctctca | 540 |
| ccaaccgcga | gggagattat | gacacgagca | ctggcaagtt | cacctgcaaa | gtccccgggc | 600 |
| tctactactt | tgtctaccac | gcgtcgcata | cagccaacct | gtgcgtgctg | ctgtaccgca | 660 |

| | | | | | | |
|------------|-------------|------------|------------|------------|------------|------|
| gcgggcgtaa | agtgggcacc | ttctgtggcc | acacgtccaa | aaccaatcag | gtcaactcgg | 720 |
| gcggtgtgct | gctgaggttg | caggtgggcg | aggaggtgtg | gctggctgtc | aatgactact | 780 |
| acgacatggg | gggcatccag | ggctctgaca | gcgtcttctc | cggcttcctg | ctcttccccg | 840 |
| actagggcgg | gcagatgcgc | tcgagcccca | cgggccttcc | acctccctca | gcttcctgca | 900 |
| tggaccaccc | ttactggcca | gtctgcatcc | ttgcctagac | cattctcccc | accagatgga | 960 |
| cttctcctcc | agggagccca | ccctgaccca | ccccactgc | acccctccc | catgggttct | 1020 |
| ctccttcttc | tgaacttctt | taggagtcac | tgcttgtgtg | gttcctggga | cacttaacca | 1080 |
| atgccttctg | gtactgccat | tctttttttt | ttttttttca | agtattggaa | gggggtggga | 1140 |
| gatatatata | taaatacatga | aatcaatata | waaaaaaaaa | aaaaaaaaaa | aaaaaaaaaa | 1200 |
| aaaaaaaaaa | aaaaaaaaaa | aaaaagggcg | gcc | | | 1233 |

<210> 190
 <211> 633
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (1)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (3)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (7)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (11)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (596)
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<220>
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<222> (611)
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 tagggaggat tgactgtgtc agggatggcg ggtggcctct ctcgctgccg gggcccttgt 120
 cagagcagcc aggctggaca gacggcctcc ctctcttcca tctgaccggc acctgctgct 180
 tcggggctta ggccaccgct ccctgtcccc agaggagata gccccagatg gactggaatg 240
 ttgtggcatg agagcgcatt tgtgcgatgg ccccgctgtg gtcccccttc tgtccctcca 300
 tctgtatgtg ttctgtgtcc cttgcatgtg tgcgtgttag agtgagcgcg tatgcatcaa 360
 ctcatggggc tcttggctgc tcacaaggca aatttgactt ggaaagactt tcatctcctt 420
 ggaaccaaga cttcctgagt cccctcacc ctggccctgt tccaccatgg ttatctgggt 480
 attgggggaat ggaaactttg ggggagtgac tttttaaaga gacacttata atttctacta 540
 ctgcactact gtccattgtg ggatgattaa acatggattt taactgtgca aaaaannnnn 600
 nnnnnnnnnn nnnnnnnnnn nnnnaaaaaa aaa 633

<210> 191
 <211> 705
 <212> DNA
 <213> Homo sapiens

| | | | | | | |
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| cgcgggagcc | tgacagagagg | acagccggcc | tgcgccggga | catgcggccc | caggagctcc | 120 |
| ccaggctcgc | gttcccgttg | ctgctgttgc | tgttgcgtgc | gctgcggccg | ccgccgtgcc | 180 |
| ctgccacacg | cgccacgcgc | ttcgaccca | cctgggagtc | cctggacgcc | cgccagctgc | 240 |
| ccgcgtggtt | tgaccaggcc | aagttcggca | tcttcatcca | ctggggagtg | ttttccgtgc | 300 |
| ccagcttcgg | tagcgagtgg | ttctggcttt | accttgtggg | ggtcagaata | ttcgtggaac | 360 |
| tggaatgcca | tagatgaggg | gcccagagg | gacattgtca | aggaacttga | ggtagccatt | 420 |
| aggaacagaa | ctgacctgcg | ttttggactg | tactattccc | tttttgaatg | gtttcatccg | 480 |
| ctcttccttg | aggatgaatc | cagttcattc | cataagcggc | aatttccagt | ttctaagaca | 540 |
| ttgccagagc | tctatgagtt | agtgaacaac | tatcagcctg | aggttctgtg | gtcggatggg | 600 |
| gacggaggag | aaccgatcat | actggaacag | cacaggcttc | ttggcctggg | tatataatga | 660 |
| aagcccagtt | cggggcacag | tagtcaccaa | tgatcggtgg | ggagc | | 705 |
| <210> 192 | | | | | | |
| <211> 2901 | | | | | | |
| <212> DNA | | | | | | |
| <213> Homo sapiens | | | | | | |
| <400> 192 | | | | | | |
| ccacgcgtcc | gtacatgctg | gccagctgaa | aaaggagact | ttcattttcac | tgactgttta | 60 |
| ttttttggtt | cactgatgtc | tgctacagat | ccagtgacag | tgctggccat | tttccatgaa | 120 |
| ctgcacgtcg | accctgacct | gtacacactc | ttgtttggag | agagtgtgtt | gaatgatgca | 180 |
| gtggccatag | tccttacata | ttctatatcc | atltacagtc | ccaaggagaa | tccaaatgca | 240 |
| tttgatgccg | cagcattctt | ccagtcctgtg | gggaatttcc | tgggaatctt | cgctggctca | 300 |
| tttgcaatgg | ggctctgcgt | tgccatcatc | acagcactgt | tgaccaaatt | taccaagctg | 360 |
| tgtgagttcc | cgatgctgga | aaccggcctg | tttttccctg | tttcttggag | tgcttccctg | 420 |
| tctgccgagg | ctgccggcct | aacagggata | gttgcctgtc | tcttctgtgg | agtcacacaa | 480 |
| gcacattata | cctacaacaa | tctgtcttcg | gattccaaaa | taagaactaa | acagttgttt | 540 |
| gaatttatga | actttttggc | ggagaacgtc | atcttctgtt | acatgggcct | ggcactgttc | 600 |
| acgtttccaga | atcatatctt | taatgctctt | tttatacttg | gagcctttct | agcaattttt | 660 |
| gttgccagag | cctgcaacat | atatccccct | tccttccctc | tgaatctagg | ccgaaaacag | 720 |
| aagatccccct | ggaactttca | gcacatgatg | atgtttttcag | gtttgcgagg | agcgatcgca | 780 |
| tttgcccttag | ctattcggaa | cacagaatct | cagcccaaac | aaatgatgtt | taccactacg | 840 |
| ctgctcctcg | tgttcttcac | tgtctgggta | ttttggagg | gaacaacccc | catgttgact | 900 |
| tggtcttcaga | tcagagttgg | cgtggacctg | gatgaaaatc | tgaaggagga | ccctcctca | 960 |
| caacaccagg | aagcaataaa | cttgataaaa | aacatgacga | aagcagagag | tgctcggctc | 1020 |
| ttcagaatgt | ggtatagctt | tgaccacaag | tatctgaaac | caattttaac | ccactctggg | 1080 |
| cctccgctga | ctacaacatt | acctgaatgg | tgtggtccga | tttccaggct | gcttaccagt | 1140 |
| cctcaagcct | atggggaaca | gctaaaagag | gatgatgtgg | aatgcattgt | aaaccaggat | 1200 |
| gaactagcca | taaatattaca | ggagcaagcc | tcctcaccct | gcagtcctcc | tgcaaggcta | 1260 |
| ggctctggacc | agaaagcttc | acccagagcg | ccaggcaagg | aaaacattta | tgaggggagac | 1320 |
| ctcgccctgg | gaggctatga | actcaagctt | gagcaaacct | tgggtcaatc | ccagttgaat | 1380 |
| taattggcat | gaagagtaca | gatgtaatca | caagtaatgc | aagactcact | gaggaataca | 1440 |
| agccaagctg | atgaggcagt | acagggggaga | ggctggaaaa | catattaaga | gcataaattg | 1500 |
| gagagaatca | aagcctttgtc | acatggatcc | tctggtgcct | gaagaaatga | gatttttatta | 1560 |
| tcctctctcta | ttatgcaaat | gaatttagtt | ttttgacagc | agccattctg | attactggat | 1620 |
| tggtctgggg | ggggatgggg | gtatcaggag | tctagctgct | ggaggatggg | acagctgtgc | 1680 |
| tgggtcttca | gggcatttct | gctgcgaatg | cggctctcca | ggcccttcac | ttctattctg | 1740 |
| gatttttatc | cctccattaa | ggagagttta | aaaataaaaag | aaagcttctg | agagtaaaca | 1800 |
| ttttgtcctc | aagctgaagg | gaatgcmcag | ctatttagta | agtgataagt | ttcttatttt | 1860 |
| gaggacttga | ctccccattg | ctctcagtga | ccccaggcca | gagcccagag | aagtgttccg | 1920 |
| taccactgct | tgatggtttc | ccagagccca | cactgagttg | aagaacctat | tgttcttctt | 1980 |
| ggcatccttc | ttatgctact | tctcccatcg | ctcaaagggg | ttgcctatgg | ctgggtgtgc | 2040 |
| cctgccctaa | atgcagcacc | actttcaagc | ttagtaggac | cattccaaga | aaaccagggt | 2100 |
| tcttctcccc | ataccacgtt | gtgcctgaag | aacaagcctt | cccgtccttg | cctgcatgtg | 2160 |
| agtcacttct | tggtctgtga | gcaggtcccc | ccctccccgc | gatatgctgg | agggtaggat | 2220 |
| tctgcagcct | gtgttgctct | ctacctggga | gcagactgtg | caggagcccc | aacctgtcct | 2280 |
| ccaattccag | cttaccagc | tgatgagcag | tgacaggagca | gggcgagagg | aacagagcca | 2340 |
| atgatgtgtg | ggttacactg | aggagccaag | gacagggcct | caggctctcc | ccttacaagg | 2400 |
| cgtggctcat | ggcctgcatt | ccagagacca | acatgatagc | ttttaattca | gctgcatgac | 2460 |
| ctgtgccttt | taagccataa | agatacctca | agcctagcac | ctcttgaaat | ccagatgttc | 2520 |
| atattagact | cgaaaaaata | ggctccaggc | ctaggtgccc | aggctatgat | gagttctgct | 2580 |
| ttgaaggagg | tagggaatga | catcttccct | ggacccaaag | cttaaaagta | atgtatgctt | 2640 |
| tgctgaccac | tgtttggttag | gccttaaaca | acattcactg | tggtggtatc | aggcacactg | 2700 |

| | | | | | | |
|------------|------------|------------|------------|------------|------------|------|
| ctatgtgcat | caattatttt | tttgctttcc | aaacagaatc | tctggggcac | aagttttaca | 2760 |
| ctcaagctaa | gtataacttt | gtcatttcag | gtaaatatga | caagtgggtg | agcatgaagt | 2820 |
| tttctaattt | gacttaatcc | taataaattt | ttgttacaaa | gtaaaaaaaa | aaaaaaaaaa | 2880 |
| aaaaaaaaaa | aaaaaaaaaa | a | | | | 2901 |

<210> 193
 <211> 611
 <212> DNA
 <213> Homo sapiens

<220>
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 <222> (598)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (611)
 <223> n equals a,t,g, or c

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|-------------|------------|-------------|------------|------------|------------|-----|
| <400> 193 | | | | | | |
| cctaagcact | ttcacctctg | ttaccttggt | gaacatgac | tctattgcat | ttcatgcccc | 60 |
| ttaagacagt | ttcataatta | tgaaaatagt | tgtagggat | ttccaaggg | aacaacatca | 120 |
| gtatttacac | aaggaaggcc | tttgatattt | taaaatttct | actgtagcta | taattgggtc | 180 |
| ccattgkttat | ttctaatact | ataaatttgt | gcattctttt | tctttatcca | cttttatgga | 240 |
| agatgggtgtg | ttttaataac | ttttttttaa | cttagctttt | gattttggat | attttgctca | 300 |
| ttgattacca | gtgatttttt | cttttctttac | aggagctttt | aagtccacag | tttccctgtg | 360 |
| catagtgtct | tagctgactc | ctaaaagttt | tgctatgcag | tggttgktaa | tcactcccag | 420 |
| gcttttctac | tttccattat | tacttctgkg | gcttgggagt | gktaaawttc | ttttwatttc | 480 |
| aattttggkg | awgggcargg | tcttgcttca | twactcargc | cgaatgcatg | gkgscaatat | 540 |
| ggsttamcaa | agcctgrctt | tcaagggtta | gctatcctcc | cccttaccct | cccagganct | 600 |
| gggcctacgg | n | | | | | 611 |

<210> 194
 <211> 3111
 <212> DNA
 <213> Homo sapiens

| | | | | | | |
|-------------|-------------|------------|------------|-------------|-------------|------|
| <400> 194 | | | | | | |
| gcgctgtgcc | tgcatatcat | ccaccaccac | cctagcccag | ccttcccact | gccccaggaa | 60 |
| aagctcttct | cctggccacc | tctgcccccc | agcacctcaa | acttgcatgg | ctgggctgtg | 120 |
| gcctctgcgg | ccaggaagcc | tgacactagg | cacccccag | gcgagagcta | gtgggggtga | 180 |
| gaggggcccc | tgccagacag | cccttggggg | tcgttgcamt | ttaagaaata | ggatytgtgg | 240 |
| tgtattccag | ggggcctgat | ggacaccttt | ccggggcgtc | tgacagctgc | ctgcccgtgc | 300 |
| ccgctgcag | tggttgagga | cgggagtggc | ccttcggctc | ccgagctccc | tctggggacg | 360 |
| gctgggtcac | tgtctccagt | tctcaatggc | caacgaagg | gcttggaaac | acctaacctt | 420 |
| gcaagtttta | ccgccttttg | aggaacacaa | atcggagaac | aaacccagg | ttcaggcggtg | 480 |
| ttttctgtga | atgttggtatg | atgaattttt | gtctcttctg | gtggagctgt | gcctggccct | 540 |
| gtaggcccag | ggttggtctg | aaggtgacat | ctgtgtttcg | ttttagctga | ggttggcaga | 600 |
| aacgttccca | aactccccca | gccctggacc | ccagcagatg | aggaaacggc | cccatttact | 660 |
| gaccccgccc | ccttttcgag | gttatgtctc | cctggtcagc | tcctcacgta | attgggggtg | 720 |
| gagggaaaagc | atgggtggtgc | cctggggcgt | ccctgtgtga | acgcaggcaa | aagcagccca | 780 |
| gtccccctca | ctgcttgagc | taacactgac | acctcttttg | tgtgagcaca | aaagccacgt | 840 |
| cccaagccac | ctggccccgat | tccacagatg | tatgtgcggc | cagtgaactc | cccaggagtg | 900 |
| tggagggggt | ggtgaggagg | agcacctggg | ctctcttacc | ctctcctcac | agaagtacct | 960 |
| gaaactaggt | ctggggcact | cccaatgcag | cgcttgtca | gccaagggtg | gcaggcaggg | 1020 |
| actgtggcag | cttatgtcca | aaggagccc | ccatgcacag | gaagccacag | ggttcctctt | 1080 |
| gtttcccccg | ctaacttcag | cctctcrtct | gctgtctcyg | gctgaggggac | tagaggacat | 1140 |
| ctcggtcggt | tgaggggcat | ggccagtcgt | ggcaggccgg | ccttcagcgt | ccggtcaggg | 1200 |
| aagcgtgcag | cccaaatggg | cacttgcatg | ggagccacag | aggagygtcc | ctggggattg | 1260 |
| ttgggaccat | gctgccccca | ctcccgcttt | tggtggggct | ctaagttctg | gaagggtgtg | 1320 |
| gcacagaggg | tgctcatggg | actcgcagtc | agctctcagc | actgggtggg | agggcggttg | 1380 |
| cttgtccaga | atggggacgt | ggggcagcca | cccctgcccc | gcgagagcgc | agacaccgtg | 1440 |
| tgaggggaca | gcagcccttg | gtgcaaagcc | agagactgat | cctgggtctg | acgggtgaag | 1500 |
| agggaaagacc | caaggctggg | tggcgtggct | cgtgaatcca | cttagaattc | ttggcttgtg | 1560 |
| tcgcatactg | ggtgtcacgg | cacacattta | ctctgcattg | tccccgtctt | tcccatcgcc | 1620 |

| | | | | | | |
|-------------|-------------|------------|-------------|-------------|------------|------|
| tagcggtttgg | ggaggaacag | ggagagagct | tcggggcgctc | tgtctccgtg | ctctcctgcc | 1680 |
| tccaccgcct | tgggttttgc | tcctgctgga | ggcagggcac | ctgctgcgac | ccagattctt | 1740 |
| ctgcaggatg | tgtctgtctt | tgtcacggtg | gacagagggt | gacatcatag | gagcagctcg | 1800 |
| ctggccagaa | ggggatgggg | gcacccctgt | gcctcactca | gctcctgctg | ctcttaggga | 1860 |
| aaggaggcct | gggtcaagcc | agcatcccc | tggtaaagac | ccccgcaggc | caccaggcat | 1920 |
| tctggacacg | cacacacaca | cacacacaca | cacacacaca | caaaaacttca | cagcaggcca | 1980 |
| gctgcagtga | cttgtcatca | agagtcacct | cagctgcgcc | ccccctccat | cctttcctat | 2040 |
| gagaagccac | tgctttgggg | gcgccggcta | gaaaaagtag | ggtgcggtgg | ccaggagggc | 2100 |
| ccctgccgcg | cgggggggctg | ggtctgggtg | agtcgctgct | ttcccagagg | cagcgcaggg | 2160 |
| atccggggaa | gctgcggcag | ggagcgggyg | ccggcttcgt | ggctctgagg | tgtaacgggg | 2220 |
| gtrggctccc | tccttcggag | gacatcgtct | gtgtccagg | cagaaagtgg | cccaggaagg | 2280 |
| gggcagtttc | tgtcgcgggt | ccgggtgggg | cgcggccgcg | gtgcggctcg | tgcagcgtgg | 2340 |
| ccaatgcgcg | gcgcgcgcgg | gggacagagc | aggaggcggt | ctgtcacctc | ggccactgct | 2400 |
| gacctgggct | ggcctccccc | agccctcccc | tggcggagcg | gcagcgatgc | tacaggccta | 2460 |
| agttattgtt | tgcataaaaa | gaatcatgtt | ccctgtgtac | atttaagaaa | aaaacaaaaa | 2520 |
| aacggaaatg | tcagaattgt | atggaaataa | aacttgtttg | aaaatttgga | atagtgtctg | 2580 |
| tgccagctta | tttttctggt | acttgtattt | tcacatgtta | aatgatcttt | atatatgttg | 2640 |
| aattaacaaa | tattttgagt | ttctgagaaa | aaacaaaaa | tattaatggt | attgaaatgt | 2700 |
| gttagtagtc | tggctgtgtg | cccaaaattc | tgtttcgcag | caaaagtga | gacctgtatg | 2760 |
| taaagaaagt | ataacaatta | tttctttgta | ttttaggggc | tttaaccgga | acatcgtcta | 2820 |
| gctggtgtta | ggaatgtttg | cttaatttcc | agactttttt | ttaaaaacac | atcgtggggt | 2880 |
| ttttgaggct | ccaacctgat | tagtgcattg | tcagccctca | atgaaggctg | aggcatctct | 2940 |
| gactgagggt | tttttgtttg | gttttgtttt | ttaaaatcat | gtatttgcta | caaagtattg | 3000 |
| tactgtcttc | aatgggaatg | gtgtaaaaaa | caaaaggcct | tatgtgatct | gtatcatagt | 3060 |
| taataaatga | atcttgtaaa | aaaaaaccca | cgcgtccgcc | cacgcgtccg | c | 3111 |

<210> 195

<211> 490

<212> DNA

<213> Homo sapiens

<400> 195

| | | | | | | |
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| tggcaggagt | gtatgtgagt | gtgtgtgtgc | atacatgtgt | gtgtatgtgt | gtgcatacat | 60 |
| gtgtgtgtat | gtgtgtgcat | acgtgtgtgt | gtgtgcatgc | atgtgtgtgg | gcgcattgtg | 120 |
| gcatgtgtgt | gtgtgagtgt | gtgtgttggg | gaggaggcat | ggcccttggg | aaggctctgt | 180 |
| caggttggaa | gccacactcc | ctccctcag | catggagggt | ggcgtgtgct | tggaggccta | 240 |
| tcgccaggag | gctgagaccc | accggcgcca | catsaacagt | gcctttatga | cctttgtggt | 300 |
| cctggacgca | gatgaccagc | cccagttgct | gccctggatt | cggccccagc | ccggcgatgg | 360 |
| tgagcggcgg | taccgagagg | ccagtgccag | aaagaagatc | cgcctggaca | ggaagtacat | 420 |
| cgtgtcctgt | aagcagacag | agggtcccc | ctccgtcccc | tgggacccta | gcaaccagg | 480 |
| gtacctgagc | | | | | | 490 |

<210> 196

<211> 1527

<212> DNA

<213> Homo sapiens

<400> 196

| | | | | | | |
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| tttgcatacct | ggtagcatgc | ctttatcggg | gagtgggtgt | gaggggaaggc | ggggaccgct | 60 |
| ggcagggtgga | ggggcagtat | ggttccagga | cccactcccc | gtagttcttg | gtggtgccc | 120 |
| gcgggcgctg | gggtgccgac | agggagggca | cgtagtctga | tgccctccac | agtggctcca | 180 |
| ccccgtaccg | gttccctgtt | agcacgtatt | ccttgccccg | gattggcctg | tctttccaca | 240 |
| gcgcgtctcc | ccaccgggtg | ctgggggcct | ggtactgggc | agggacgatg | gggtcatgcc | 300 |
| aggcgggtct | ccgcagggtg | tgggtgtagg | ccgatggcat | gctgcactca | cgggtgtggt | 360 |
| agcagctgtg | cmagcgggtg | taggcytcgc | ggaaggggct | ggccggggcc | cgtggcagg | 420 |
| tgtaccaggc | ttcccaggcg | tcagagttag | tcaggcytgt | gtaccacagc | tkgccggctg | 480 |
| cgtcccgtcc | catgggcgtg | tacttccagc | gtgtggcctg | cctgatggyt | ggtggccagc | 540 |
| gggaaccctc | cagggacagg | tagtcatcgc | tgtacagcgg | tgctgggaag | ctggcctcga | 600 |
| gggtccccgc | ggggatacac | ggcgggtgac | cctcttgcc | gaggggttgc | atgtttgcct | 660 |
| ggatcccccg | ggctcctgcc | agaaggcctc | taaggccacc | gttgracagc | ataaaggcca | 720 |
| cccagtgctc | cggcaaccac | gctgaccact | ccctcctccc | agctgcgggg | tgaggtggcc | 780 |
| tcgaggggaag | ggctggagag | tcgttctgag | tatttaacaa | ctgggggtga | cacagtgtgg | 840 |
| gtgggcaagg | ccaggggccac | tgccagggtg | ggtccgtggc | cctgagcccc | cagctctatg | 900 |
| cacccccccac | ctgggggtctg | gcttctccat | ctccacaccc | ccttgagggg | cttctgtctc | 960 |
| cccctgcccc | ttcgatcgca | ggaggcagtg | cctggccggg | gtcgcaggca | cctgtcacc | 1020 |
| cagctcctca | ctcctcacc | actcacatcc | agtcgggttg | taaaatacac | ccaggatgag | 1080 |

| | | | | | | |
|-------------|------------|------------|-------------|------------|------------|------|
| acctgcacgc | agtgggtcac | agcagcacga | tttgtgacag | cccgaggcgg | agaacaccga | 1140 |
| acacccagtg | aaggtgaggg | gatcagcacg | gcgcccgcac | cgtgctggaa | cgagactcag | 1200 |
| ccacaaggag | gtgcgacgtc | tgacccaggc | cacagtgcgg | atgsaccttg | aggatgtcac | 1260 |
| gctcagtgag | agacaccaga | cacagaaggg | tacgctgtga | tcccacttct | atgaaatgtc | 1320 |
| caggacagac | caatccacag | aatcagggar | aggattccgtg | ggtgccggga | ctggggaggg | 1380 |
| ggacctgggg | gtgactaggt | gacataatgg | ggacagggct | gccttttggg | tgatgagaat | 1440 |
| gttctgggaat | cagatgggat | ggctgcacgg | cgtggtgaag | gtactgaacg | ccacctcact | 1500 |
| gtaagacggg | agatttttga | ttttacc | | | | 1527 |

<210> 197

<211> 3746

<212> DNA

<213> Homo sapiens

<400> 197

| | | | | | | |
|-------------|-------------|-------------|--------------|-------------|-------------|------|
| gcggcgctg | tccctgggtg | cgcggtgag | ctacgccgtg | ggccacttcc | tcaacgacct | 60 |
| gtgcgcgtcc | atgtggttca | cctacctgct | gctctacctg | cactcgggtg | gcgcctacag | 120 |
| ctcccgcggc | gcggggctgc | tgctgctgct | gggcccagggtg | gccgacgggc | tgtgcacacc | 180 |
| gctcgtgggc | tacgaggccg | accgcgcgcg | cagctgctgc | gcccgcctacg | gcccgcgcaa | 240 |
| ggcctggcac | ctggctcgga | ccgtctgctg | cctgctgtcc | ttccccttca | tcttcagccc | 300 |
| ctgcctgggc | tgtggggcgg | ccacgcccga | gtgggctgcc | ctcctctact | acggcccgtt | 360 |
| catcgtgatc | ttccagtttg | gctggggcctc | cacacagatc | tcccacctca | gcctcatccc | 420 |
| ggagctcgct | accaacgacc | atgagaaggt | ggagctcacg | gcactcaggt | atgcgttcac | 480 |
| cgtggtggcc | aacatcaccc | tctacggcgc | cgcttggctc | ctgctgcacc | tgcagggtc | 540 |
| gtcgcgggtg | gagccacccc | aagacatcag | catcagcgac | cagctggggg | gccaggacgt | 600 |
| gcccgtgttc | cggaacctgt | ccctgctggg | ggtgggtgtc | ggcgccgtgt | tctcactgct | 660 |
| attccacctg | ggcaccgcgg | agaggcgccg | gccgcctgctg | gaggagccag | gcgagcacac | 720 |
| ccccctgttg | gcccctgcca | cggcccagcc | cctgctgctc | tgggaagcact | ggctccggga | 780 |
| gcccgttttc | taccaggtgg | gcatactgta | catgaccacc | aggctcatcg | tgaacctgtc | 840 |
| ccagacctac | atggccatgt | acctcaccta | ctcgctccac | ctgcccaga | agttcatcgc | 900 |
| gaccattccc | ctgggtgatgt | acctcagcgg | cttcttgtcc | tccttccctca | tgaagcccat | 960 |
| caacaagtgc | attgggagga | acatgacctc | cttctcaggc | ctcctgggtga | tcctggcctt | 1020 |
| tgccgcctgg | gtggcgctgg | cggagggact | gggtgtggcc | gtgtacgcag | cggctgtgct | 1080 |
| gctgggtgct | ggctgtgcca | ccatcctcgt | cacctcgctg | gccatgacgg | cgcacctcat | 1140 |
| cggcccccc | acgaacagcg | gagcgcttcg | gtacggctcc | atgagcttct | tggataaggt | 1200 |
| ggccaatggg | ctggcagtc | tggccatcca | gagcctgcac | ccttgcccc | cagagctctg | 1260 |
| ctgcaggggc | tgcgtgagct | tttaccactg | ggcgtagggtg | gctgtgacgg | gcggcggtggg | 1320 |
| cgtggccgct | gcccgtgtgtc | tctgtagcct | cctgctgtgg | ccgaccgcgc | tgcgacgctc | 1380 |
| ccgaggcgga | gaacaccgaa | caccagtgta | aggtgagggg | atcagcacgg | cgccgccacc | 1440 |
| gtgctggaac | gagactcagc | cacaaggagg | tgcgaagctc | tgacccaggc | cacagtgcgg | 1500 |
| atgcaccttg | aggatgtcac | gctcagtgag | agacaccaga | cacagaaggg | tacgctgtga | 1560 |
| tcccacttct | atgaaatgtc | caggacagac | caatccacag | aatcaggag | aggattcgtg | 1620 |
| ggtgccggga | ctggggaggg | ggacctgggg | gtgactagggt | gacataatgg | ggacagggtc | 1680 |
| gccttctggg | tgatgagaat | gttctggaat | cagatgggat | ggctgcacgg | cgtggtgaag | 1740 |
| gtactgaacg | ccacctcact | gtaagacggg | agatttttga | ttttaccaca | ataaacaaaa | 1800 |
| caaaacaaaa | caaaaaaaa | mmmaaaaaac | atccagaaac | ctcctgccct | gcccgtcccc | 1860 |
| tcctctggct | gggcccggcc | ttgggtgggg | gcggagctgc | accctgggtc | ccgcttcccc | 1920 |
| tgccttgttc | aggtcmccac | agatacgacc | ctgcctttmc | catctggaca | cgcaccagg | 1980 |
| agctccactc | cctcggggta | ggtgcccaag | tcctccctga | ggcccacaag | gcccgtgcacg | 2040 |
| ccctgccctc | ctctcctcac | tctgttcttc | ccgcatacca | ggtgccgtcc | tgccccaggg | 2100 |
| cctttgcatg | gctgtgcoct | ttgcctctca | cccaggcgctc | cctgccttct | ccagccctgg | 2160 |
| ctgaaatgcc | aggcttgtgg | tgagcctctg | atccaaggcc | gcccctcccc | aaggccccct | 2220 |
| ccccaccctt | gtgacgccac | ctcctcactt | cctcataagc | ttctctgtct | ctgggtctgtg | 2280 |
| tccccatgc | cagctccaca | tgggccagggt | ctgctcgggt | tcacatctc | caatgccag | 2340 |
| gatggggcct | gccccagctc | cttcaccctc | ttctcaggca | ccgcgcaaga | gcgagcctca | 2400 |
| aaaccacctg | gggcctcctg | gctgccagga | ccccacagc | ctcccctgca | gcccccgcc | 2460 |
| ccccggcctc | ctggctccct | cagccacttc | ccagccattc | ctcctgttct | ctccgcccag | 2520 |
| accccgggga | ggcaccagca | ccccctgggc | caggctcctg | cctcctgcac | ctctcatcgc | 2580 |
| agaacctatg | gcagcctgag | tttttcaatt | ctcttccctt | ctcactgcac | cagctacatt | 2640 |
| ccaggatcaa | cagaaaagtt | gcagcccgc | ctgcggggcc | cttgggtcagc | ctccccctcc | 2700 |
| atctgggcgt | ctcccaacca | ctgccagggt | cgccccagga | agcgatggcc | ccactggcct | 2760 |
| tcgtctgcct | gtcgggtgga | gctgacagca | gaggcacctg | ccccagcgct | gctgagtggc | 2820 |
| ccccgtgccc | cgcaaagcct | gacgtacact | ccccgggggc | ccctccacct | cctctcagct | 2880 |
| gtcctggggc | atgggggaacc | aattccccca | tttctacacg | agccctggcc | catcatcatg | 2940 |
| ggaccctccc | accacggcct | tcacccccct | tgtctgtgct | ctcctggccc | catctggcca | 3000 |
| gcccctggggg | tgaactcagc | ccagcagtg | ccaccctccc | tccctgatgg | tgtcaaccga | 3060 |

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gcacctcttc cctggaacag ggccgtccag ctggagcgca gggacttgcc tggagtccag 3120
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<210> 198

<211> 91

<212> PRT

<213> Homo sapiens

<400> 198

```

Met Val Leu Arg Gly Trp Gly Leu Ala Trp Ser Leu Ser Pro Val Val
  1              5              10              15
Cys Gly Tyr Ser Gly Asp Met Lys Gly Val Cys Trp Gly Arg Ser Asp
              20              25              30
His Ser Leu Leu Pro Ser Glu Ile Leu Leu Pro Pro Ala Pro Cys Pro
              35              40              45
Ser Ser Ala Val Leu His Asn Pro Pro Pro Thr Pro His Leu Pro Ser
  50              55              60
Pro Val Leu Val Arg Ile Gln Glu Ala Pro Thr Trp Ala Gln Arg Ser
  65              70              75              80
Ser Leu Gly Ala Ser Pro Leu His Lys Gly Asp
              85              90

```

<210> 199

<211> 49

<212> PRT

<213> Homo sapiens

<400> 199

```

Met Ser Cys Thr Leu Leu Ile Cys Thr Val Val Leu Gly Val Thr Thr
  1              5              10              15
Pro Ala Ile Gly Pro Ala Ala Pro Ser Leu Leu Ala Thr Pro Pro Gln
              20              25              30
Ala Ala Ala Ala Thr Met Gln Pro Arg Leu Gly Arg Ala Ala Gly Ala
              35              40              45
Ala

```

<210> 200

<211> 95

<212> PRT

<213> Homo sapiens

<400> 200

```

Met Val Pro Cys Arg Lys Thr Leu Leu Phe Leu Trp Val Gly Ser Leu

```

108

| | | | |
|---|----|----|----|
| 1 | 5 | 10 | 15 |
| Cys Arg Asp Val Gly Ser Trp Ser Gly Trp Pro Phe Gly Leu Ser Thr | 20 | 25 | 30 |
| Ala Thr Gln Pro Arg Leu Arg Leu Gly Lys Gln Thr Gly Ala Gly Gln | 35 | 40 | 45 |
| Ala Arg Arg Ala Cys Arg Thr Val Ile Leu Arg Cys Gly Ser Cys Cys | 50 | 55 | 60 |
| Arg Gly Arg Arg Thr Gly Ser Val Val Ala Trp Ser Ser Leu Pro Gln | 65 | 70 | 75 |
| Arg Thr Ser Ala Ala Glu Leu Arg Trp Arg Pro Trp Gly Pro Val | 85 | 90 | 95 |

<210> 201
 <211> 175
 <212> PRT
 <213> Homo sapiens

<400> 201
 Met Ala Thr Pro Ser Gly Leu Gly Ala Leu Leu Leu Leu Leu Leu
 1 5 10 15
 Pro Thr Ser Gly Gln Glu Lys Pro Thr Glu Gly Pro Arg Asn Thr Cys
 20 25 30
 Leu Gly Ser Asn Asn Met Tyr Asp Ile Phe Asn Leu Asn Asp Lys Ala
 35 40 45
 Leu Cys Phe Thr Lys Cys Arg Gln Ser Gly Ser Asp Ser Cys Asn Val
 50 55 60
 Glu Asn Leu Gln Arg Tyr Trp Leu Asn Tyr Glu Ala His Leu Met Lys
 65 70 75 80
 Glu Gly Leu Thr Gln Lys Val Asn Thr Pro Phe Leu Lys Ala Leu Val
 85 90 95
 Gln Asn Leu Ser Thr Asn Thr Ala Glu Asp Phe Tyr Phe Ser Leu Glu
 100 105 110
 Pro Ser Gln Val Pro Arg Gln Val Met Lys Asp Glu Asp Lys Pro Pro
 115 120 125
 Asp Arg Val Arg Leu Pro Lys Ser Leu Phe Arg Ser Leu Pro Gly Asn
 130 135 140
 Arg Ser Val Val Arg Leu Ala Val Thr Ile Leu Asp Ile Gly Pro Gly
 145 150 155 160
 Thr Leu Phe Lys Val Arg Thr Gln Gly Ser Ser Lys Val Lys Cys
 165 170 175

<210> 202
 <211> 126
 <212> PRT
 <213> Homo sapiens

<400> 202

109

Met Ala Ala Phe Ala Thr Ala His Leu Leu Tyr Val Trp Ala Phe Gly
 1 5 10 15
 Phe Ser Pro Leu Gln Pro Gly Leu Leu Leu Ile Ile Leu Ala Pro
 20 25 30
 Gly Pro Tyr Leu Ser Leu Val Leu Gln His Leu Glu Pro Asp Met Val
 35 40 45
 Leu Pro Val Ala Ala Tyr Gly Leu Ile Leu Met Ala Met Leu Trp Arg
 50 55 60
 Gly Leu Ala Gln Gly Gly Ser Ala Gly Trp Gly Ala Leu Leu Phe Thr
 65 70 75 80
 Leu Ser Asp Gly Val Leu Ala Trp Asp Thr Phe Ala Gln Pro Leu Pro
 85 90 95
 His Ala His Leu Val Ile Met Thr Thr Tyr Tyr Ala Ala Gln Leu Leu
 100 105 110
 Ile Thr Leu Ser Ala Leu Arg Ser Pro Val Pro Lys Thr Asp
 115 120 125

<210> 203
 <211> 187
 <212> PRT
 <213> Homo sapiens

<400> 203
 Met Trp Cys Ala Ser Pro Val Ala Val Val Ala Phe Cys Ala Gly Leu
 1 5 10 15
 Leu Val Ser His Pro Val Leu Thr Gln Gly Gln Glu Ala Gly Gly Arg
 20 25 30
 Pro Gly Ala Asp Cys Glu Val Cys Lys Glu Phe Leu Asn Arg Phe Tyr
 35 40 45
 Lys Ser Leu Ile Asp Arg Gly Val Asn Phe Ser Leu Asp Thr Ile Glu
 50 55 60
 Lys Glu Leu Ile Ser Phe Cys Leu Asp Thr Lys Gly Lys Glu Asn Arg
 65 70 75 80
 Leu Cys Tyr Tyr Leu Gly Ala Thr Lys Asp Ala Ala Thr Lys Ile Leu
 85 90 95
 Ser Glu Val Thr Arg Pro Met Ser Val His Met Pro Ala Met Lys Ile
 100 105 110
 Cys Glu Lys Leu Lys Lys Leu Asp Ser Gln Ile Cys Glu Leu Lys Tyr
 115 120 125
 Glu Lys Thr Leu Asp Leu Ala Ser Val Asp Leu Arg Lys Met Arg Val
 130 135 140
 Ala Glu Leu Lys Gln Ile Leu His Ser Trp Gly Glu Glu Cys Arg Ala
 145 150 155 160
 Cys Ala Glu Lys Thr Asp Tyr Val Asn Leu Ile Gln Glu Leu Ala Pro
 165 170 175
 Lys Tyr Ala Ala Thr His Pro Lys Thr Glu Leu

110

180

185

<210> 204
 <211> 38
 <212> PRT
 <213> Homo sapiens

<400> 204
 Met Thr Trp Gly Thr Lys Ala Thr Trp Tyr Leu Ala Ser Ser Ser Ser
 1 5 10 15
 Cys Gly Ser Tyr Cys Pro Pro Pro Cys Trp Trp Ala Ser Ser Gly Cys
 20 25 30
 Thr Gly Pro His Arg Thr
 35

<210> 205
 <211> 163
 <212> PRT
 <213> Homo sapiens

<400> 205
 Met Gly Gly Met Ile Ile Val Leu Leu Ile Cys Ile Val Trp Phe Pro
 1 5 10 15
 Leu Leu Phe Met Ser Leu Ile Lys Ser Val Ala Gly Val Ile Asn Gln
 20 25 30
 Pro Leu Asp Val Ser Val Thr Ile Thr Leu Gly Gly Tyr Gln Pro Ile
 35 40 45
 Phe Thr Met Ser Ala Gln Gln Ser Gln Leu Lys Ile Met Asp Gln Gln
 50 55 60
 Ser Phe Asn Lys Phe Ile Gln Ala Phe Ser Arg Asp Thr Gly Ala Met
 65 70 75 80
 Gln Phe Leu Glu Asn Tyr Glu Lys Glu Asp Ile Thr Val Ala Glu Leu
 85 90 95
 Glu Gly Asn Ser Asn Ser Leu Trp Thr Ile Ser Pro Pro Ser Lys Gln
 100 105 110
 Lys Met Ile His Glu Leu Leu Asp Pro Asn Ser Ser Phe Ser Val Val
 115 120 125
 Phe Ser Trp Ser Ile Gln Arg Asn Leu Ser Leu Gly Ala Lys Ser Glu
 130 135 140
 Ile Ala Thr Asp Lys Leu Ser Phe Pro Leu Lys Asn Ile Asn Ser Lys
 145 150 155 160
 Glu Tyr Arg

<210> 206
 <211> 369
 <212> PRT
 <213> Homo sapiens

111

<400> 206

```

Met Ala Phe Lys Leu Leu Ile Leu Leu Ile Gly Thr Trp Ala Leu Phe
 1           5           10           15

Phe Arg Lys Arg Arg Ala Asp Met Pro Arg Val Phe Val Phe Arg Ala
          20           25           30

Leu Leu Leu Val Leu Ile Phe Leu Phe Val Val Ser Tyr Trp Leu Phe
 35           40           45

Tyr Gly Val Arg Ile Leu Asp Ser Arg Asp Arg Asn Tyr Gln Gly Ile
 50           55           60

Val Gln Tyr Ala Val Ser Leu Val Asp Ala Leu Leu Phe Ile His Tyr
 65           70           75           80

Leu Ala Ile Val Leu Leu Glu Leu Arg Gln Leu Gln Pro Met Phe Thr
          85           90           95

Leu Gln Val Val Arg Ser Thr Asp Gly Glu Ser Arg Phe Tyr Ser Leu
          100          105          110

Gly His Leu Ser Ile Gln Arg Ala Ala Leu Val Val Leu Glu Asn Tyr
          115          120          125

Tyr Lys Asp Phe Thr Ile Tyr Asn Pro Asn Leu Leu Thr Ala Ser Lys
          130          135          140

Phe Arg Ala Ala Lys His Met Ala Gly Leu Lys Val Tyr Asn Val Asp
          145          150          155          160

Gly Pro Ser Asn Asn Ala Thr Gly Gln Ser Arg Ala Met Ile Ala Ala
          165          170          175

Ala Ala Arg Arg Arg Asp Ser Ser His Asn Glu Leu Tyr Tyr Glu Glu
          180          185          190

Ala Glu His Glu Arg Arg Val Lys Lys Arg Lys Ala Arg Leu Val Val
          195          200          205

Ala Val Glu Glu Ala Phe Ile His Ile Gln Arg Leu Gln Ala Glu Glu
          210          215          220

Gln Gln Lys Ala Pro Gly Glu Val Met Asp Pro Arg Glu Ala Ala Gln
          225          230          235          240

Ala Ile Phe Pro Ser Met Ala Arg Ala Leu Gln Lys Tyr Leu Arg Ile
          245          250          255

Thr Arg Gln Gln Asn Tyr His Ser Met Glu Ser Ile Leu Gln His Leu
          260          265          270

Ala Phe Cys Ile Thr Asn Gly Met Thr Pro Lys Ala Phe Leu Glu Arg
          275          280          285

Tyr Leu Ser Ala Gly Pro Thr Leu Gln Tyr Asp Lys Asp Arg Trp Leu
          290          295          300

Ser Thr Gln Trp Arg Leu Val Ser Asp Glu Ala Val Thr Asn Gly Leu
          305          310          315          320

Arg Asp Gly Ile Val Phe Val Leu Lys Cys Leu Asp Phe Ser Leu Val
          325          330          335

Val Asn Val Lys Lys Ile Pro Phe Ile Ile Leu Ser Glu Glu Phe Ile

```

112

| | | |
|---------------------------------|---------------------|-------------|
| 340 | 345 | 350 |
| Asp Pro Lys Ser His Lys Phe Val | Leu Arg Leu Gln Ser | Glu Thr Ser |
| 355 | 360 | 365 |

Val

<210> 207
 <211> 85
 <212> PRT
 <213> Homo sapiens

<400> 207
 Met Asp Thr Tyr Phe Ile Leu Trp Ala Ile Pro Val Thr Ile Ile Ile
 1 5 10 15
 Cys Phe Ser Trp Leu Glu Tyr Ser Gln Thr Trp Ala Leu Gly Ala Ser
 20 25 30
 Cys Ser Leu Pro Gln Cys Pro Phe Asp Val Met Leu Ser Leu Phe Leu
 35 40 45
 Val His Pro Tyr Phe Pro Thr Val Trp Asp His Leu Cys Phe Pro His
 50 55 60
 Pro Ser Pro Glu Ser Ser Pro Phe Ser Lys Cys Ser Leu Val Ala Trp
 65 70 75 80
 Leu Glu Asn Gly Ala
 85

<210> 208
 <211> 172
 <212> PRT
 <213> Homo sapiens

<400> 208
 Met His Gly Ala Arg Leu Phe Val Cys Leu Phe Val Cys Phe Arg Gln
 1 5 10 15
 Ser Cys Tyr Val Ala Gln Ala Gly Val Gln Trp His Asn His Ser Ser
 20 25 30
 Leu Gln Pro Leu Ser Pro Gly Phe Lys Arg Phe Phe Cys Leu Asn Leu
 35 40 45
 Pro Ser Ser Trp Asp Tyr Arg His Met Ala Thr Cys Pro Trp Leu Ile
 50 55 60
 Phe Val Phe Leu Val Glu Met Glu Phe Arg His Val Gly Gln Ala Gly
 65 70 75 80
 Leu Gly Leu Leu Thr Ser Ser Asp Leu Pro Ala Leu Ala Phe Gln Ser
 85 90 95
 Ala Gly Ile Thr Gly Leu Ser His His Ala Trp Pro Gly Arg Phe Leu
 100 105 110
 Lys Lys Val Ile Glu Ile Cys Ser Cys Pro Val Pro Arg Gly Ser His
 115 120 125

113

Ala Gly Leu Phe Ser Ala Pro Gly Leu Pro Cys Glu Ser Gly Gly Ala
130 135 140

Ala Val Leu Leu Gln Glu Gly Gln Thr Pro Val Gln Glu Ala Arg Thr
145 150 155 160

His His Gln Leu Val Gly Gly Gln Gly Arg Leu Cys
165 170

<210> 209
<211> 829
<212> PRT
<213> Homo sapiens

<400> 209
Met Ala Pro Ala Gly Cys Cys Cys Cys Cys Cys Phe Trp Gly Gly Ala
1 5 10 15

Val Ala Ala Ala Gly Ala Ala Arg Arg Val Leu Leu Leu Leu Leu Leu
20 25 30

Gly Val Leu Ser Ala Arg Leu Arg Pro Gly Ala Leu Ala Thr Glu His
35 40 45

Tyr Ser Pro Leu Ala Leu Leu Lys Gln Glu Leu Gln His Arg Gln Gln
50 55 60

Gln Glu Ala Pro Ala Gly Gly Gly Gly Cys Ser Pro Gln Ser Gly Asp
65 70 75 80

Trp Gly Asp Gln Tyr Ser Ala Glu Cys Gly Glu Ser Ser Phe Leu Asn
85 90 95

Phe His Asp Ser Asp Cys Glu Pro Lys Gly Ser Ser Pro Cys Asp Ser
100 105 110

Leu Leu Ser Leu Asn Thr Glu Lys Ile Leu Ser Gln Ala Lys Ser Ile
115 120 125

Ala Glu Gln Lys Arg Phe Pro Phe Ala Thr Asp Asn Asp Ser Thr Asn
130 135 140

Glu Glu Leu Ala Ile Ala Tyr Val Leu Ile Gly Ser Gly Leu Tyr Asp
145 150 155 160

Glu Ala Ile Arg His Phe Ser Thr Met Leu Gln Glu Glu Pro Asp Leu
165 170 175

Val Ser Ala Ile Tyr Gly Arg Gly Ile Ala Tyr Gly Lys Lys Gly Leu
180 185 190

His Ile Leu Ser Pro Leu Gly Arg Ile Asn Glu Ala Val Asn Asp Leu
195 200 205

Thr Lys Ala Ile Gln Leu Gln Pro Ser Ala Arg Leu Tyr Arg His Arg
210 215 220

Gly Thr Leu Tyr Phe Ile Ser Glu Asp Tyr Ala Thr Ala His Glu Asp
225 230 235 240

Phe Gln Gln Ser Leu Glu Leu Asn Lys Asn Gln Pro Ile Ala Met Leu
245 250 255

Tyr Lys Gly Leu Thr Phe Phe His Arg Gly Leu Leu Lys Glu Ala Ile

| 260 | | | | | 265 | | | | | 270 | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Glu | Ser | Phe | Lys | Glu | Ala | Leu | Lys | Gln | Lys | Val | Asp | Phe | Ile | Asp | Ala |
| | | 275 | | | | | 280 | | | | | 285 | | | |
| Tyr | Lys | Ser | Leu | Gly | Gln | Ala | Tyr | Arg | Glu | Leu | Gly | Asn | Phe | Glu | Ala |
| | 290 | | | | | 295 | | | | | 300 | | | | |
| Ala | Thr | Glu | Ser | Phe | Gln | Lys | Ala | Leu | Leu | Leu | Asn | Gln | Asn | His | Val |
| 305 | | | | | | 310 | | | | | 315 | | | | 320 |
| Gln | Thr | Leu | Gln | Leu | Arg | Gly | Met | Met | Leu | Tyr | His | His | Gly | Ser | Leu |
| | | | | 325 | | | | | 330 | | | | | 335 | |
| Gln | Glu | Ala | Leu | Lys | Asn | Phe | Lys | Arg | Cys | Leu | Gln | Leu | Glu | Pro | Tyr |
| | | | 340 | | | | | 345 | | | | | 350 | | |
| Asn | Glu | Val | Cys | Gln | Tyr | Met | Lys | Gly | Leu | Ser | His | Val | Ala | Met | Gly |
| | | 355 | | | | | 360 | | | | | 365 | | | |
| Gln | Phe | Tyr | Glu | Gly | Ile | Lys | Ala | Gln | Thr | Lys | Val | Met | Leu | Asn | Asp |
| | 370 | | | | | 375 | | | | | 380 | | | | |
| Pro | Leu | Pro | Gly | Gln | Lys | Ala | Ser | Pro | Glu | Tyr | Leu | Lys | Val | Lys | Tyr |
| 385 | | | | | | 390 | | | | | 395 | | | | 400 |
| Leu | Arg | Glu | Tyr | Ser | Arg | Tyr | Leu | His | Ala | His | Leu | Asp | Thr | Pro | Leu |
| | | | | 405 | | | | | 410 | | | | | 415 | |
| Thr | Glu | Tyr | Asn | Ile | Asp | Val | Asp | Leu | Pro | Gly | Ser | Phe | Lys | Asp | His |
| | | | 420 | | | | | 425 | | | | | 430 | | |
| Trp | Ala | Lys | Asn | Leu | Pro | Phe | Leu | Ile | Glu | Asp | Tyr | Glu | Glu | Gln | Pro |
| | | 435 | | | | | 440 | | | | | 445 | | | |
| Gly | Leu | Gln | Pro | His | Ile | Lys | Asp | Val | Leu | His | Gln | Asn | Phe | Glu | Ser |
| | 450 | | | | | 455 | | | | | 460 | | | | |
| Tyr | Lys | Pro | Glu | Val | Gln | Glu | Leu | Ile | Cys | Val | Ala | Asp | Arg | Leu | Gly |
| 465 | | | | | | 470 | | | | | 475 | | | | 480 |
| Ser | Leu | Met | Gln | Tyr | Glu | Thr | Pro | Gly | Phe | Leu | Pro | Asn | Lys | Arg | Ile |
| | | | | 485 | | | | | 490 | | | | | 495 | |
| His | Arg | Ala | Met | Gly | Leu | Ala | Ala | Leu | Glu | Val | Met | Gln | Ala | Val | Gln |
| | | | 500 | | | | | 505 | | | | | 510 | | |
| Arg | Thr | Trp | Thr | Asn | Ser | Lys | Val | Arg | Met | Asn | Gly | Lys | Thr | Arg | Leu |
| | | 515 | | | | | 520 | | | | | 525 | | | |
| Met | Gln | Trp | Arg | Asp | Met | Phe | Asp | Ile | Ala | Val | Lys | Trp | Arg | Arg | Ile |
| | 530 | | | | | 535 | | | | | 540 | | | | |
| Ala | Asp | Pro | Asp | Gln | Pro | Val | Leu | Trp | Leu | Asp | Gln | Met | Pro | Ala | Arg |
| 545 | | | | | | 550 | | | | | 555 | | | | 560 |
| Ser | Leu | Ser | Arg | Gly | Phe | Asn | Asn | His | Ile | Asn | Leu | Ile | Arg | Gly | Gln |
| | | | | 565 | | | | | 570 | | | | | 575 | |
| Val | Ile | Asn | Met | Arg | Tyr | Leu | Glu | Tyr | Phe | Glu | Lys | Ile | Leu | His | Phe |
| | | | 580 | | | | | 585 | | | | | 590 | | |
| Ile | Lys | Asp | Arg | Ile | Leu | Val | Tyr | His | Gly | Ala | Asn | Asn | Pro | Lys | Gly |
| | | 595 | | | | | 600 | | | | | 605 | | | |
| Leu | Leu | Glu | Val | Arg | Glu | Ala | Leu | Glu | Lys | Val | His | Lys | Val | Glu | Asp |

115

| 610 | | | | | 615 | | | | | 620 | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Leu | Pro | Ile | Met | Lys | Gln | Phe | Asn | Thr | Lys | Thr | Lys | Asp | Gly | Phe |
| 625 | | | | | 630 | | | | | 635 | | | | | 640 |
| Thr | Val | Asn | Thr | Lys | Val | Pro | Ser | Leu | Lys | Asp | Gln | Gly | Lys | Glu | Tyr |
| | | | | 645 | | | | | 650 | | | | | 655 | |
| Asp | Gly | Phe | Thr | Ile | Thr | Ile | Thr | Gly | Asp | Lys | Val | Gly | Asn | Ile | Leu |
| | | | 660 | | | | | 665 | | | | | 670 | | |
| Phe | Ser | Val | Glu | Thr | Gln | Thr | Thr | Glu | Glu | Arg | Thr | Gln | Leu | Tyr | His |
| | | | 675 | | | | | 680 | | | | | 685 | | |
| Ala | Glu | Ile | Asp | Ala | Leu | Tyr | Lys | Asp | Leu | Thr | Ala | Lys | Gly | Lys | Val |
| | | | | | | | | | | | | | | | |
| Leu | Ile | Leu | Ser | Ser | Glu | Phe | Gly | Glu | Ala | Asp | Ala | Val | Cys | Asn | Leu |
| 705 | | | | | 710 | | | | | 715 | | | | | 720 |
| Ile | Leu | Ser | Leu | Val | Tyr | Tyr | Phe | Tyr | Asn | Leu | Met | Pro | Leu | Ser | Arg |
| | | | | 725 | | | | | 730 | | | | | 735 | |
| Gly | Ser | Ser | Val | Ile | Ala | Tyr | Ser | Val | Ile | Val | Gly | Ala | Leu | Met | Ala |
| | | | 740 | | | | | 745 | | | | | 750 | | |
| Ser | Gly | Lys | Glu | Val | Ala | Gly | Lys | Ile | Pro | Lys | Gly | Lys | Leu | Val | Asp |
| | | | 755 | | | | 760 | | | | | 765 | | | |
| Phe | Glu | Ala | Met | Thr | Ala | Pro | Gly | Ser | Glu | Ala | Phe | Ser | Lys | Val | Ala |
| | | | 770 | | | | 775 | | | | | 780 | | | |
| Lys | Ser | Trp | Met | Asn | Leu | Lys | Ser | Ile | Ser | Pro | Ser | Tyr | Lys | Thr | Leu |
| 785 | | | | | 790 | | | | | 795 | | | | | 800 |
| Pro | Ser | Val | Ser | Glu | Thr | Phe | Pro | Thr | Leu | Arg | Ser | Met | Ile | Glu | Val |
| | | | | 805 | | | | | 810 | | | | | 815 | |
| Leu | Asn | Thr | Asp | Ser | Ser | Pro | Arg | Cys | Leu | Lys | Lys | Leu | | | |
| | | | 820 | | | | | 825 | | | | | | | |

<210> 210
 <211> 108
 <212> PRT
 <213> Homo sapiens

<400> 210
 Met Thr Ser Gln Asn Leu Trp Val Ile Val Val Ile Ala Asn Ser Ile
 1 5 10 15
 Leu Val Ile Val Ala Gln Tyr Arg Asp Glu Gly Asn Arg Phe Cys Asn
 20 25 30
 Gln Met Ile Leu Gly Ser Glu Ser Thr Leu Pro Leu Thr Ser Tyr Met
 35 40 45
 Thr Ser Ser Asn Phe His His Leu Ser Met Leu Gln Phe Pro His Arg
 50 55 60
 Gln Asp Gly Cys Gly Gly Arg Gly Thr Thr Val Gln Ile His His Pro
 65 70 75 80
 Lys Phe Lys Met Leu Gln Asn Leu Gly Arg Ala Trp Trp Leu Ile Pro
 85 90 95

116

Val Ile Pro Ala Leu Trp Glu Val Lys Val Asp Gly
 100 105

<210> 211
 <211> 153
 <212> PRT
 <213> Homo sapiens

<400> 211
 Met Met Trp Leu Leu Leu Thr Thr Thr Cys Leu Ile Cys Gly Thr Leu
 1 5 10 15
 Asn Ala Gly Gly Phe Leu Asp Leu Glu Asn Glu Val Asn Pro Glu Val
 20 25 30
 Trp Met Asn Thr Ser Glu Ile Ile Ile Tyr Asn Gly Tyr Pro Ser Glu
 35 40 45
 Glu Tyr Glu Val Thr Thr Glu Asp Gly Tyr Ile Leu Leu Val Asn Arg
 50 55 60
 Ile Pro Tyr Gly Arg Thr His Ala Arg Ser Thr Gly Pro Arg Pro Val
 65 70 75 80
 Val Tyr Met Gln His Ala Leu Phe Ala Asp Asn Ala Tyr Trp Leu Glu
 85 90 95
 Asn Tyr Ala Asn Gly Ser Leu Gly Phe Leu Leu Ala Asp Ala Gly Tyr
 100 105 110
 Asp Val Trp Met Gly Asn Ser Arg Gly Asn Thr Trp Ser Arg Arg His
 115 120 125
 Lys Thr Leu Ser Glu Thr Asp Glu Lys Phe Trp Ala Phe Ser Phe Asp
 130 135 140
 Glu Met Ala Asn Met Ile Ser Gln Glu
 145 150

<210> 212
 <211> 87
 <212> PRT
 <213> Homo sapiens

<400> 212
 Met Arg Phe Ile Trp Leu Met Phe Leu Gln Ala Val Gln Ala Ser Gly
 1 5 10 15
 Lys Gly Leu Arg Lys Leu Pro His Thr Val Glu Asp Glu Gly Glu Pro
 20 25 30
 Glu Cys Ala Asp Tyr Met Val Arg Glu Trp Lys Gln Glu Arg Gly Ala
 35 40 45
 Gly Gly Ala Arg Ile Phe Ser Thr Ile Ser Ser Trp Met Ser Thr Val
 50 55 60
 Ala His Ala Cys Asn Pro Ser Thr Leu Gly Ala Gln Asp Gly Arg Ile
 65 70 75 80
 Thr Ser Ala Gln Glu Phe Asn

117

85

<210> 213
 <211> 90
 <212> PRT
 <213> Homo sapiens

<400> 213
 Met Asp Arg Arg Arg Met Ala Leu Arg Pro Gly Ser Arg Arg Pro Thr
 1 5 10 15
 Ala Phe Phe Phe His Ser Arg Trp Leu Val Pro Asn Leu Leu Ala Phe
 20 25 30
 Phe Leu Gly Leu Ser Gly Ala Gly Pro Ile His Leu Pro Met Pro Trp
 35 40 45
 Pro Asn Gly Arg Arg His Arg Val Leu Asp Pro His Thr Gln Leu Ser
 50 55 60
 Thr His Glu Ala Pro Gly Arg Trp Lys Pro Val Ala Pro Arg Arg Met
 65 70 75 80
 Lys Ala Cys Pro Gln Val Leu Leu Glu Trp
 85 90

<210> 214
 <211> 34
 <212> PRT
 <213> Homo sapiens

<400> 214
 Met Met Ser Ile His Cys Val Gln Pro Leu Leu Pro Leu Phe Leu Pro
 1 5 10 15
 Ser Ser Tyr Phe Lys Gln Phe Leu Leu Leu Pro Trp Thr Phe Gly Val
 20 25 30
 Ala Leu

<210> 215
 <211> 245
 <212> PRT
 <213> Homo sapiens

<400> 215
 Met Phe Leu Leu Phe Leu Leu Thr Cys Glu Leu Ala Ala Glu Val Ala
 1 5 10 15
 Ala Glu Val Glu Lys Ser Ser Asp Gly Pro Gly Ala Ala Gln Glu Pro
 20 25 30
 Thr Trp Leu Thr Asp Val Pro Ala Ala Met Glu Phe Ile Ala Ala Thr
 35 40 45
 Glu Val Ala Val Ile Gly Phe Phe Gln Asp Leu Glu Ile Pro Ala Val
 50 55 60
 Pro Ile Leu His Ser Met Val Gln Lys Phe Pro Gly Val Ser Phe Gly

118

65 70 75 80
 Ile Ser Thr Asp Ser Glu Val Leu Thr His Tyr Asn Ile Thr Gly Asn
 85 90 95
 Thr Ile Cys Leu Phe Arg Leu Val Asp Asn Glu Gln Leu Asn Leu Glu
 100 105 110
 Asp Glu Asp Ile Glu Ser Ile Asp Ala Thr Lys Leu Ser Arg Phe Ile
 115 120 125
 Glu Ile Asn Ser Leu His Met Val Thr Glu Tyr Asn Pro Val Ala Ser
 130 135 140
 Pro Glu Tyr Glu Glu Asn Met His Arg Tyr Gln Lys Ala Ala Lys Leu
 145 150 155 160
 Phe Gln Gly Lys Ile Leu Phe Ile Leu Val Asp Ser Gly Met Lys Glu
 165 170 175
 Asn Gly Lys Val Ile Ser Phe Phe Lys Leu Lys Glu Ser Gln Leu Pro
 180 185 190
 Ala Leu Ala Ile Tyr Gln Thr Leu Asp Asp Glu Trp Asp Thr Leu Pro
 195 200 205
 Thr Ala Glu Val Ser Val Glu His Val Gln Asn Phe Cys Asp Gly Phe
 210 215 220
 Leu Ser Gly Lys Leu Leu Lys Glu Asn Arg Glu Ser Glu Gly Lys Thr
 225 230 235 240
 Pro Lys Val Glu Leu
 245

<210> 216
 <211> 459
 <212> PRT
 <213> Homo sapiens

<400> 216
 Met Phe Pro Leu His Leu Ala Val Leu Phe Gly Phe Ser Asp Cys Cys
 1 5 10 15
 Arg Lys Leu Leu Ser Ser Gly Gln Leu Tyr Ser Ile Val Ser Ser Leu
 20 25 30
 Ser Asn Glu His Val Leu Ser Ala Gly Phe Asp Ile Asn Thr Pro Asp
 35 40 45
 Asn Leu Gly Arg Thr Cys Leu His Ala Ala Ala Ser Gly Gly Asn Val
 50 55 60
 Glu Cys Leu Asn Leu Leu Leu Ser Ser Gly Ala Asp Leu Arg Arg Arg
 65 70 75 80
 Asp Lys Phe Gly Arg Thr Pro Leu His Tyr Ala Ala Ala Asn Gly Ser
 85 90 95
 Tyr Gln Cys Ala Val Thr Leu Val Thr Ala Gly Ala Gly Val Asn Glu
 100 105 110
 Ala Asp Cys Lys Gly Cys Ser Pro Leu His Tyr Ala Ala Ala Ser Asp
 115 120 125

Thr Tyr Arg Arg Ala Glu Pro His Thr Pro Ser Ser His Asp Ala Glu
 130 135 140
 Glu Asp Glu Pro Leu Lys Glu Ser Arg Arg Lys Glu Ala Phe Phe Cys
 145 150 155 160
 Leu Glu Phe Leu Leu Asp Asn Gly Ala Asp Pro Ser Leu Arg Asp Arg
 165 170 175
 Gln Gly Tyr Thr Ala Val His Tyr Ala Ala Ala Tyr Gly Asn Arg Gln
 180 185 190
 Asn Leu Glu Leu Leu Leu Glu Met Ser Phe Asn Cys Leu Glu Asp Val
 195 200 205
 Glu Ser Thr Ile Pro Val Ser Pro Leu His Leu Ala Ala Tyr Asn Gly
 210 215 220
 His Cys Glu Ala Leu Lys Thr Leu Ala Glu Thr Leu Val Asn Leu Asp
 225 230 235 240
 Val Arg Asp His Lys Gly Arg Thr Ala Leu Phe Leu Ala Thr Glu Arg
 245 250 255
 Gly Ser Thr Glu Cys Val Glu Val Leu Thr Ala His Gly Ala Ser Ala
 260 265 270
 Leu Ile Lys Glu Arg Lys Arg Lys Trp Thr Pro Leu His Ala Ala Ala
 275 280 285
 Ala Ser Gly His Thr Asp Ser Leu His Leu Leu Ile Asp Ser Gly Glu
 290 295 300
 Arg Ala Asp Ile Thr Asp Val Met Asp Ala Tyr Gly Gln Thr Pro Leu
 305 310 315 320
 Met Leu Ala Ile Met Asn Gly His Val Asp Cys Val His Leu Leu Leu
 325 330 335
 Glu Lys Gly Ser Thr Ala Asp Ala Ala Asp Leu Arg Gly Arg Thr Ala
 340 345 350
 Leu His Arg Gly Ala Val Thr Gly Cys Glu Asp Cys Leu Ala Ala Leu
 355 360 365
 Leu Asp His Asp Ala Phe Val Leu Cys Arg Asp Phe Lys Gly Arg Thr
 370 375 380
 Pro Ile His Leu Ala Ser Ala Cys Gly His Thr Ala Val Leu Arg Thr
 385 390 395 400
 Leu Leu Gln Ala Ala Leu Ser Thr Asp Pro Leu Asp Ala Gly Val Asp
 405 410 415
 Tyr Ser Gly Tyr Ser Pro Met His Trp Ala Ser Tyr Thr Gly His Glu
 420 425 430
 Asp Cys Leu Glu Leu Leu Leu Glu His Ser Pro Phe Ser Tyr Leu Glu
 435 440 445
 Gly Asn Pro Phe Thr Pro Ser Leu Cys Ser Asp
 450 455

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<210> 217
<211> 110
<212> PRT
<213> Homo sapiens
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```

<400> 217
Met Lys Arg Tyr Ile Ile Ser Leu Gln Ser Pro Leu Ser His Ser Ser
  1                               5          10          15

Met Trp Pro Ala Tyr Leu Leu Pro Ile Met Leu Leu Ile His Leu Gln
          20          25          30

Ala Ile Cys His Gln Ile Lys Lys Gln Gln Thr Glu Gly Gln Ser Gln
          35          40          45

Asp Val Leu Thr His His Cys Asn Phe Leu Leu Glu Met Ile Pro Phe
  50          55          60

Arg Lys Arg Leu Val Glu Ile Gly Val Lys Gly Thr Leu Gln Ile Ser
  65          70          75          80

Pro Val Leu Ser Tyr Phe Gln Leu Tyr Arg Gln Glu Gln Phe Lys Ser
          85          90          95

Lys Glu Phe Ser Arg Phe Leu Gln Cys His Lys Ala Val Ser
          100          105          110

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<210> 218
<211> 107
<212> PRT
<213> Homo sapiens
```

```

<400> 218
Met  Pro  Pro  Pro  Phe  Leu  Arg  Lys  Pro  Leu  Ile  Leu  Cys  Val  Phe  Leu
  1          5          10          15

Pro  Thr  Glu  Gly  Asn  Cys  Gly  Gly  Ser  Ser  Leu  Ala  Phe  Leu  Leu  Asn
          20          25          30

Phe  Ala  Gly  Asn  Ser  Pro  Gln  Phe  Leu  Ser  Glu  Val  Arg  Thr  Val  His
          35          40          45

Tyr  Gln  Arg  Asp  Trp  Thr  Leu  Tyr  Pro  Leu  Ala  Lys  Trp  Glu  Lys  Ile
  50          55          60

Leu  Pro  Ala  His  Ser  Thr  Pro  Pro  Trp  Pro  Ser  Pro  Thr  Pro  His  Pro
  65          70          75          80

Gln  Gln  His  Phe  His  Gly  Asn  Pro  Asp  Gly  Arg  Val  Val  Leu  Trp  Leu
          85          90          95

Ser  Cys  Asp  Arg  Leu  Ala  Phe  Ile  Leu  Glu  Ser
          100          105

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<210> 219
<211> 428
<212> PRT
<213> Homo sapiens
```

<400> 219
Met Gly Pro Pro Pro Gly Ala Gly Val Ser Cys Arg Gly Gly Cys Gly
1 5 10 15

Phe Ser Arg Leu Leu Ala Trp Cys Phe Leu Leu Ala Leu Ser Pro Gln
 20 25 30
 Ala Pro Gly Ser Arg Gly Ala Glu Ala Val Trp Thr Ala Tyr Leu Asn
 35 40 45
 Val Ser Trp Arg Val Pro His Thr Gly Val Asn Arg Thr Val Trp Glu
 50 55 60
 Leu Ser Glu Glu Gly Val Tyr Gly Gln Asp Ser Pro Leu Glu Pro Val
 65 70 75 80
 Ala Gly Val Leu Val Pro Pro Asp Gly Pro Gly Ala Leu Asn Ala Cys
 85 90 95
 Asn Pro His Thr Asn Phe Thr Val Pro Thr Val Trp Gly Ser Thr Val
 100 105 110
 Gln Val Ser Trp Leu Ala Leu Ile Gln Arg Gly Gly Gly Cys Thr Phe
 115 120 125
 Ala Asp Lys Ile His Leu Ala Tyr Glu Arg Gly Ala Ser Gly Ala Val
 130 135 140
 Ile Phe Asn Phe Pro Gly Thr Arg Asn Glu Val Ile Pro Met Ser His
 145 150 155 160
 Pro Gly Ala Val Asp Ile Val Ala Ile Met Ile Gly Asn Leu Lys Gly
 165 170 175
 Thr Lys Ile Leu Gln Ser Ile Gln Arg Gly Ile Gln Val Thr Met Val
 180 185 190
 Ile Glu Val Gly Lys Lys His Gly Pro Trp Val Asn His Tyr Ser Ile
 195 200 205
 Phe Phe Val Ser Val Ser Phe Phe Ile Ile Thr Ala Ala Thr Val Gly
 210 215 220
 Tyr Phe Ile Phe Tyr Ser Ala Arg Arg Leu Arg Asn Ala Arg Ala Gln
 225 230 235 240
 Ser Arg Lys Gln Arg Gln Leu Lys Ala Asp Ala Lys Lys Ala Ile Gly
 245 250 255
 Arg Leu Gln Leu Arg Thr Leu Lys Gln Gly Asp Lys Glu Ile Gly Pro
 260 265 270
 Asp Gly Asp Ser Cys Ala Val Cys Ile Glu Leu Tyr Lys Pro Asn Asp
 275 280 285
 Leu Val Arg Ile Leu Thr Cys Asn His Ile Phe His Lys Thr Cys Val
 290 295 300
 Asp Pro Trp Leu Leu Glu His Arg Thr Cys Pro Met Cys Lys Cys Asp
 305 310 315 320
 Ile Leu Lys Ala Leu Gly Ile Glu Val Asp Val Glu Asp Gly Ser Val
 325 330 335
 Ser Leu Gln Val Pro Val Ser Asn Glu Ile Ser Asn Ser Ala Ser Ser
 340 345 350
 His Glu Glu Asp Asn Arg Ser Glu Thr Ala Ser Ser Gly Tyr Ala Ser
 355 360 365

122

Val Gln Gly Thr Asp Glu Pro Pro Leu Glu Glu His Val Gln Ser Thr
 370 375 380

Asn Glu Ser Leu Gln Leu Val Asn His Glu Ala Asn Ser Val Ala Val
 385 390 395 400

Asp Val Ile Pro His Val Asp Asn Pro Thr Phe Glu Glu Asp Glu Thr
 405 410 415

Pro Asn Gln Glu Thr Ala Val Arg Glu Ile Lys Ser
 420 425

<210> 220
 <211> 124
 <212> PRT
 <213> Homo sapiens

<400> 220
 Met Leu Thr Gln Ser Gln Gln Val Leu Arg Gly Ile Leu Leu Phe Leu
 1 5 10 15

Gln Asn Ile Leu Gln Val Ser Trp Gly Ser Pro Leu Ala Leu Ala Ser
 20 25 30

Pro Pro Ser Pro Ser Leu Gln Pro Gly Asn Gly Leu Ala Ser Ser Leu
 35 40 45

Leu Ala Leu Gln Pro Gly Leu Ala Gly Pro Trp Ala Gly Pro Gln Glu
 50 55 60

Pro Ser Pro Ala Met Cys Phe Pro Lys Lys Arg Ser Leu Trp Pro Asn
 65 70 75 80

Leu Arg Lys Gln Trp Ala Ser Ile His Ile Asn Asp Pro Arg Gly Thr
 85 90 95

Leu Cys Pro Arg Cys Thr Gly Cys Asn Gln Arg Gly Ser Gly Gly Ser
 100 105 110

Gly Leu Ile Trp Arg Asp Arg Phe Tyr His His Pro
 115 120

<210> 221
 <211> 87
 <212> PRT
 <213> Homo sapiens

<400> 221
 Met Thr Trp Ser Phe Cys Phe Ala Leu Phe Cys Phe Val Leu Phe Phe
 1 5 10 15

Ala Ala Ser Leu Ile Gly Tyr Ile Leu Leu Pro Ser Ala Ser Pro Arg
 20 25 30

Asn His Arg Arg Pro Asn Asn Glu Ala Arg Val Gly Thr Pro Gly Gln
 35 40 45

Leu Asp Asp Glu Leu Lys Gly Arg Gln Pro Leu Ala Ser Arg Leu Glu
 50 55 60

Thr Ser Gln Cys Thr Gln Gly Leu Leu Ala Ser Arg Pro Ser Gly Val

123

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65              70              75              80
Ser Lys Ala Leu Leu Tyr Pro
      85

<210> 222
<211> 84
<212> PRT
<213> Homo sapiens

<400> 222
Met Glu Trp Gln Phe Gly Lys Pro Ser Phe Leu Leu Ser Leu Leu Met
  1              5              10              15

Leu Leu Val Leu Glu Trp Lys Ala Leu Cys Gly Val Arg Leu Gly His
      20              25              30

Leu Gly Leu Gln Val Pro Asn Pro Ser Leu Lys Ser Thr Cys Leu Trp
      35              40              45

Pro Leu Arg Ser Leu Cys Pro Trp Arg Leu Tyr Pro Ile Lys Ile Met
      50              55              60

Ile Ser Leu Pro Leu Pro Ser Leu Gln Leu Pro Ser Ser Pro His Arg
      65              70              75              80

Pro Phe Gln Leu

```

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<210> 223
<211> 76
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (43)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 223
Met Pro Leu Pro Pro Lys Trp Pro Pro Leu Leu Thr Ala Leu Leu Cys
 1                5                10                15
His Leu Leu Ser Thr Ser Ser Pro Leu Leu Ile Ile Leu Pro Asn His
      20                25                30
Arg Ser Asp His Pro Leu Thr Asp Leu Ser Xaa Leu Ser Ile Ala Tyr
      35                40                45
Lys Asn Glu Asn Gln Thr Thr Glu Leu Ser Met Thr Val Lys Ala Leu
      50                55                60
His Leu Ala Ser Ile Tyr Cys Ile Leu His Ala Ser
      65                70                75

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<210> 224
<211> 142
<212> PRT
<213> Homo sapiens
```

124

<400> 224

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Met Leu Trp Thr Thr Leu Thr Gly Val Ser Leu Ala Leu Phe Pro Val
 1             5             10             15

Ala Gln Ala Pro Thr Ala Leu Val Ala Leu Ala Val Ala Tyr Gly Phe
                20             25             30

Thr Ser Gly Ala Leu Ala Pro Leu Ala Phe Ser Val Leu Pro Glu Leu
          35             40             45

Ile Gly Thr Arg Arg Ile Tyr Cys Gly Leu Gly Leu Leu Gln Met Ile
 50             55             60

Glu Ser Ile Gly Gly Leu Leu Gly Pro Pro Leu Ser Gly Tyr Leu Arg
 65             70             75             80

Asp Val Thr Gly Asn Tyr Thr Ala Ser Phe Val Val Ala Gly Ala Phe
                85             90             95

Leu Leu Ser Gly Ser Gly Ile Leu Leu Thr Leu Pro His Phe Phe Cys
          100             105             110

Phe Ser Thr Thr Thr Ser Gly Pro Gln Asp Leu Val Thr Glu Ala Leu
          115             120             125

Asp Thr Lys Val Pro Leu Pro Lys Glu Gly Leu Glu Glu Asp
          130             135             140

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<210> 225

<211> 84

<212> PRT

<213> Homo sapiens

<400> 225

```

Met Phe Leu Ser Gly Lys Pro Gly Glu Ser Tyr Leu Ser His Leu Pro
 1             5             10             15

Cys Leu Phe Phe Phe Phe Phe Phe Gly Trp Ser Cys Cys Leu Asp
          20             25             30

Asp Ala Phe Thr Met Gln Glu Arg Val Phe Val Lys Asp Ile Phe Glu
          35             40             45

Asp Trp Leu Phe His Ile Val Leu His Ser Leu Thr Val Ala Lys Cys
          50             55             60

Thr Val Asp Phe His Asp His Cys Ile Phe Leu Val Ile Glu Met Tyr
          65             70             75             80

Leu Leu Cys Phe

```

<210> 226

<211> 88

<212> PRT

<213> Homo sapiens

<400> 226

```

Met Phe Pro Ile Leu Ser Ile Thr Thr Leu Ser Ile Leu Ala Phe Phe
 1             5             10             15

Leu Trp Leu Ser Val Thr Ser His Phe Tyr Arg Gln Lys Thr Gly Phe

```

| | | | | | | | | | | | | | | | | |
|-------------------|-------------------|-------------------|-----|-------------------|-------------------|-------------------|-------------------|-----|-----|-------------------|-------------------|-------------------|-----|-----|-------------------|--|
| 20 | | | | | | | 25 | | | | | 30 | | | | |
| His | His | Ser ₃₅ | Pro | Ser | Phe | Tyr | Leu ₄₀ | Ile | Val | Gln | Ile | Trp ₄₅ | Asp | Thr | Tyr | |
| Ala | Asp ₅₀ | Ile | Val | Ala | Ser | Glu ₅₅ | Tyr | Val | Phe | Pro | Trp ₆₀ | Arg | Lys | Thr | Leu | |
| Ser ₆₅ | Ser | Arg | Glu | Gln | Cys ₇₀ | Leu | Ser | Val | Val | Pro ₇₅ | Val | Ala | Phe | Ser | Leu ₈₀ | |
| Ile | Asp | Phe | Ile | Ser ₈₅ | Lys | Val | Ser | | | | | | | | | |

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<210> 227
<211> 127
<212> PRT
<213> Homo sapiens
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| | | | | | | | | | | | | | | | | |
|-------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
| <400> | 227 | | | | | | | | | | | | | | | |
| Met | Met | Pro | Thr | Tyr | Ala | Ile | Cys | Met | Val | Leu | Val | Phe | Leu | Leu | Leu | |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | | |
| Val | His | Leu | His | Ile | Ile | Asn | Thr | Asn | Thr | His | Thr | His | Thr | His | Thr | |
| | | | 20 | | | | | 25 | | | | | 30 | | | |
| His | Thr | His | Thr | Gly | Leu | Leu | Pro | Glu | Pro | Tyr | Met | Leu | Tyr | Phe | Gln | |
| | | 35 | | | | | 40 | | | | | 45 | | | | |
| Phe | Leu | Ser | Val | Leu | Arg | Gly | Tyr | Ile | Leu | Ser | Arg | Trp | Thr | Asp | Arg | |
| 50 | | | | | | 55 | | | | | 60 | | | | | |
| Glu | Tyr | Thr | Trp | Ile | Ser | Thr | Lys | Ile | Tyr | Ser | Pro | Asn | Ser | Pro | Glu | |
| 65 | | | | | 70 | | | | | 75 | | | | | 80 | |
| Pro | Pro | Ala | Ser | Cys | Pro | Ser | Pro | Thr | Gln | Ser | Ile | Ser | Arg | His | Ala | |
| | | | | 85 | | | | | 90 | | | | | 95 | | |
| Val | Gln | Gly | Ser | Thr | Phe | Leu | Lys | Ala | Gln | Leu | Pro | Thr | Ser | Glu | Gln | |
| | | | 100 | | | | | 105 | | | | | 110 | | | |
| Val | Gln | Ile | His | Pro | Leu | His | Pro | Pro | Ile | His | Leu | Ser | Pro | Leu | | |
| | | 115 | | | | | 120 | | | | | 125 | | | | |

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<210> 228
<211> 83
<212> PRT
<213> Homo sapiens
```

<400> 228
Met Thr Ser Leu Ala Arg Leu Pro Cys Ser Tyr Leu Cys Leu Pro Cys
1 5 10 15
Gln Leu Ser Ser Cys Cys Ala Phe Ser Gln Pro Ile Ser Ala Leu Leu
20 25 30
Pro Ser Pro Ser Thr Pro Val Leu Leu Ser Ala Pro Arg Pro Ser Ser
35 40 45
Gln Gly Val Pro Gly Thr Arg Ser Glu Phe Pro Ser Thr Pro Phe Cys
50 55 60

126

Leu Pro Ser Phe Pro Arg Glu Ser Phe Leu Asp Ser Phe His Leu Val
 65 70 75 80

Ser Ser His

<210> 229
 <211> 114
 <212> PRT
 <213> Homo sapiens

<400> 229
 Met Ala Lys Ala Pro Phe Tyr His Leu Leu Phe Cys Phe Gly Ile Trp
 1 5 10 15
 Ser Asp Ser Tyr Ser Ser Leu Gly Leu Ala Gln Trp Arg Asn Trp Cys
 20 25 30
 Ser Tyr Cys Thr Gly Leu Cys Thr Pro Cys Asn Cys Asp Val Tyr Asp
 35 40 45
 Cys Ser Ser Cys Phe Pro Ile Leu His Phe Gln Ser Pro Arg Ala Val
 50 55 60
 Leu Ser Arg Ile Thr Ser Thr Val Asn Gln Arg Arg Asp Cys Thr Thr
 65 70 75 80
 Arg His Val Cys Trp Glu Arg Arg Lys Gly Glu Lys Pro Trp Pro Lys
 85 90 95
 Gln Ser Ile Pro Gln Ile Leu Arg His Ser Phe Val Tyr Leu Val Phe
 100 105 110
 His His

<210> 230
 <211> 81
 <212> PRT
 <213> Homo sapiens

<400> 230
 Met Arg Trp Arg Lys Pro Leu Cys Leu Trp Cys Leu Leu Thr Gln Gly
 1 5 10 15
 Glu Thr Glu Ala Gln Ala Gly Gln Pro Leu Ala Trp Gly Gly Gly Trp
 20 25 30
 Val Val Leu Arg Pro Val Thr Ser Pro Leu Gln His Pro Pro Val Asp
 35 40 45
 Pro Leu Pro Ala Pro Ala Arg Pro Glu Ser Cys Ser Gln Ala Gln Thr
 50 55 60
 Leu Ala Cys Pro Ser Gly Asp Ala Gly Gln Tyr Ser Ser Leu Gln Pro
 65 70 75 80
 Ser

127

<210> 231
 <211> 273
 <212> PRT
 <213> Homo sapiens

<400> 231
 Met Thr Ser Gly Pro Arg Gly Val Val His Phe Tyr Gly Tyr Ser Val
 1 5 10 15
 Val Ser Thr Leu Ala Leu Leu Val Ser Ile Ala Phe Pro Ile Pro Ile
 20 25 30
 Cys Gln Gln Trp Glu Pro Ser Tyr Lys Arg Val Lys Ala Leu Ser Ile
 35 40 45
 Val Gly Gly Asp Pro His Leu Ile Leu Leu Ala Ser Thr Thr Val Leu
 50 55 60
 Val Gly Ala Ile Val Ser Thr Val Gln Asn Phe Leu Phe Trp His Met
 65 70 75 80
 Lys Asp His Gly Ser Gly Glu Leu Val Met Gly Phe Ser Val Ala Leu
 85 90 95
 Ser Leu Leu Gly Glu Ile Leu Leu His Pro Phe Lys Ala Thr Leu Leu
 100 105 110
 Arg Lys Leu Ser Arg Thr Gly Leu Val Gly Leu Gly Leu Ser Cys Leu
 115 120 125
 Ala Gly Gln Leu Leu Tyr Tyr Ser Phe Leu Trp Ser Trp Trp Ser Val
 130 135 140
 Leu Pro Ile Gln Ile Leu Ser Ala Ile Ser Asn Arg Ala Leu Trp Trp
 145 150 155 160
 Ala Val Gly Ala Ser Val Glu Asp Leu Ala Thr Pro Arg Met Glu Arg
 165 170 175
 Ala Leu Ser Ala Leu Phe Arg Gly His Phe Tyr Gly Ser Gly Cys Ser
 180 185 190
 Leu Gly Ser Phe Val Gly Gly Phe Val Val Met Arg Phe Ser Leu Ala
 195 200 205
 Val Leu Tyr Gln Ala Cys Cys Val Ala Leu Leu Leu Trp Leu Ala Leu
 210 215 220
 Leu Leu Ser Ile Gln Arg Arg Leu Pro Arg Glu Arg Lys Ile Lys Tyr
 225 230 235 240
 Ser Lys Leu Leu Ser Met Glu Val Ser Asp Thr Ser Asp Ser Glu Gln
 245 250 255
 Gly Thr Glu Gln Asp Trp Leu Val Lys Ala Met Arg Glu Glu His Ser
 260 265 270

Asp

<210> 232
 <211> 112
 <212> PRT
 <213> Homo sapiens

128

<400> 232

Met Ala Ser Pro Ala Pro Ala Cys Leu Gly Ser Leu Leu Ser Trp Thr
 1 5 10 15
 Val Cys Gly Trp Gly Glu Val Val Ser Gly Pro Pro Cys Ala Val Ser
 20 25 30
 Ala Trp Gly Cys Ser Trp Ala Thr Trp Val Thr Pro Ser Val Val Val
 35 40 45
 Gln Leu Ala Pro Ser Gly Ala Val Gln Thr Pro Leu Ser Pro Glu Leu
 50 55 60
 Leu Val Ile Ser Phe Gln Leu His Ala Ala Pro Leu Gly Gln Phe Tyr
 65 70 75 80
 Phe Pro Ile Leu Gln Met Gly Lys Glu Lys Leu Arg Leu Arg Asn Met
 85 90 95
 Pro Lys Glu Ala Pro Val Pro Val Phe Cys Phe Val Leu Phe Cys Phe
 100 105 110

<210> 233

<211> 82

<212> PRT

<213> Homo sapiens

<400> 233

Met Gly Gln Leu Cys His Ser Pro Ser Cys Leu Pro Ser Gly Ala Phe
 1 5 10 15
 Cys Leu Leu Leu Ser Ser Val Leu Gly Ile Ile Val Leu Asn Ser Thr
 20 25 30
 Asp Thr Ile Ser Ser Ser His Pro Pro Leu Ser Ser Asn Leu Pro Ser
 35 40 45
 Trp Gly Tyr Thr Thr Thr Lys Ala His Leu Ser Leu Gly Leu Val Gly
 50 55 60
 Phe Ala Gly Lys Glu Asn Met Lys Glu Leu Tyr Val Glu Ser Ser Arg
 65 70 75 80
 Ser Phe

<210> 234

<211> 136

<212> PRT

<213> Homo sapiens

<400> 234

Met Ile Glu Asp Thr Met Thr Leu Leu Ser Leu Leu Gly Arg Ile Met
 1 5 10 15
 Arg Tyr Phe Leu Leu Arg Pro Glu Thr Leu Phe Leu Leu Cys Ile Ser
 20 25 30

129

Leu Ala Leu Trp Ser Tyr Phe Phe His Thr Asp Glu Val Lys Thr Ile
 35 40 45
 Val Lys Ser Ser Arg Asp Ala Val Lys Met Val Lys Gly Lys Val Ala
 50 55 60
 Glu Ile Met Gln Asn Asp Arg Leu Gly Gly Leu Asp Val Leu Glu Ala
 65 70 75 80
 Glu Phe Ser Lys Thr Trp Glu Phe Lys Asn His Asn Val Gly Gly Val
 85 90 95
 Leu His Pro Gly Pro Glu Arg Pro His Gly Gly Pro Leu Arg Ser Ser
 100 105 110
 His Gly Ser Gly Gln Gln Asp Ala Pro Val His Leu Arg Asp Leu Arg
 115 120 125
 Arg Ala Arg Gly Arg Asp Cys Ser
 130 135

<210> 235
 <211> 47
 <212> PRT
 <213> Homo sapiens

<400> 235
 Met Lys Ser Lys Phe Cys Phe Ala Ser Pro Met Arg Leu Pro Lys Ala
 1 5 10 15
 Leu Leu Ala Phe Ser Ala Cys Trp Gln Leu Leu Ser Ala Trp Leu Leu
 20 25 30
 Thr Phe Leu Pro Thr Leu Leu Thr Asn Gln Lys Lys Ser Gln Glu
 35 40 45

<210> 236
 <211> 122
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (58)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (99)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (106)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 236
 Met Phe Tyr Leu Thr His Pro Ile Lys Asn Phe Asn Met Ser Ser Arg
 1 5 10 15
 Lys Lys Lys Cys Ala Phe Tyr Ile Ile Leu Leu Leu Leu Ser Leu Ser
 20 25 30

130

Pro Gly Thr Trp Phe Thr Pro Thr Pro Thr Pro Gln Leu Thr Leu Ala
 35 40 45

Val Trp Gln Val Pro Ser Gly His Leu Xaa Arg Ala Leu Cys Ile Gln
 50 55 60

Cys Cys Pro Pro Ala Val Ala Gly Ala Val Gly Ala Ser Asp Lys Met
 65 70 75 80

His Pro Gln Pro Trp Gln Cys Leu Gln Ser Cys Pro Phe Val Asn Ser
 85 90

Gly Pro Xaa His Pro His Ala Arg Pro Xaa Thr Ala Trp Asp Ala Cys
 100 105 110

Ala Gly Gly Arg Ala Phe Leu Val Arg His
 115 120

<210> 237
 <211> 90
 <212> PRT
 <213> Homo sapiens

<400> 237
 Met Trp Phe Lys Gly Gln Leu His Phe Phe Phe Leu Phe Phe Ser Phe
 1 5 10 15

Leu Thr Phe Leu Phe Ser Ser Leu Phe Ser Ser Leu Leu Phe Leu Ser
 20 25 30

Phe Leu Phe Phe Pro Phe Phe Leu Ser Gln Gly Phe Ile Leu Ser His
 35 40 45

Arg Leu Glu Tyr Asn Gly Ile Gly Ser Leu Gln Pro Gln Thr Pro Arg
 50 55 60

Leu Lys Pro Ser Ser Gly Leu Ser Leu Leu Ser Ser Trp Asp Tyr Arg
 65 70 75 80

Cys Ala Pro Leu Pro His Ser Ala Asn Phe
 85 90

<210> 238
 <211> 33
 <212> PRT
 <213> Homo sapiens

<400> 238
 Met Pro Asn Ser Leu Leu Gly Val Phe Phe Cys Phe Val Leu Phe Cys
 1 5 10 15

Phe Val Leu Phe Cys Leu Ile Gln Ser Phe Thr Leu Ser Pro Arg Leu
 20 25 30

Glu

<210> 239
 <211> 35

131

<212> PRT
 <213> Homo sapiens

<400> 239
 Met Cys His His Ala Gln Leu Ile Phe Val Leu Leu Val Glu Thr Gly
 1 5 10 15
 Phe Cys His Val Gly Gln Ala Gly Leu Glu Leu Leu Thr Ser His Asp
 20 25 30
 Leu Arg Thr
 35

<210> 240
 <211> 82
 <212> PRT
 <213> Homo sapiens

<400> 240
 Met Leu Thr Asn Arg Ala Pro Ser Ser Phe Val Trp Phe Leu Cys Leu
 1 5 10 15
 Ala Cys His Leu Pro Ser Cys Pro Ser Ala Thr Glu Glu Phe Ala Val
 20 25 30
 Phe Ile Pro Lys Tyr His Ser Ser Arg Met Gly Ala Ala Pro Cys His
 35 40 45
 Val Leu Gly His Gly Gly Ile Lys Gly Asn Thr Cys Gln Asp Asn Ala
 50 55 60
 Gly Tyr Asp Phe Cys Arg Pro Leu Gly Leu Ala Ser Phe Leu Lys Arg
 65 70 75 80
 Gln Asp

<210> 241
 <211> 219
 <212> PRT
 <213> Homo sapiens

<400> 241
 Met Arg Pro Arg Gly Leu Pro Pro Leu Leu Val Val Leu Leu Gly Cys
 1 5 10 15
 Trp Ala Ser Val Ser Ala Gln Thr Asp Ala Thr Pro Ala Val Thr Thr
 20 25 30
 Glu Gly Leu Asn Ser Thr Glu Ala Ala Leu Ala Thr Phe Gly Thr Phe
 35 40 45
 Pro Ser Thr Arg Pro Pro Gly Thr Pro Arg Ala Pro Gly Pro Ser Ser
 50 55 60
 Gly Pro Arg Pro Thr Pro Val Thr Asp Val Ala Val Leu Cys Val Cys
 65 70 75 80
 Asp Leu Ser Pro Ala Gln Cys Asp Ile Asn Cys Cys Cys Asp Pro Asp
 85 90 95
 Cys Ser Ser Val Asp Phe Ser Val Phe Ser Ala Cys Ser Val Pro Val

132

| 100 | | | | | | | | 105 | | | | 110 | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Thr | Gly | Asp | Ser | Gln | Phe | Cys | Ser | Gln | Lys | Ala | Val | Ile | Tyr | Ser |
| | | 115 | | | | | 120 | | | | | 125 | | | |
| Leu | Asn | Phe | Thr | Ala | Asn | Pro | Pro | Gln | Arg | Val | Phe | Glu | Leu | Val | Asp |
| | 130 | | | | | 135 | | | | | 140 | | | | |
| Gln | Ile | Asn | Pro | Ser | Ile | Phe | Cys | Ile | His | Ile | Thr | Asn | Tyr | Lys | Pro |
| 145 | | | | | 150 | | | | | 155 | | | | | 160 |
| Ala | Leu | Ser | Phe | Ile | Asn | Pro | Glu | Val | Pro | Asp | Glu | Asn | Asn | Phe | Asp |
| | | | | 165 | | | | | 170 | | | | | 175 | |
| Thr | Leu | Met | Lys | Thr | Ser | Asp | Gly | Phe | Thr | Leu | Asn | Ala | Glu | Tyr | Met |
| | | | 180 | | | | | 185 | | | | | 190 | | |
| Phe | Pro | Ser | Gln | Pro | Asn | Trp | Ile | Phe | Leu | Leu | Leu | Leu | Asn | Met | Ser |
| | 195 | | | | | | 200 | | | | | | 205 | | |
| Met | Gly | Phe | Leu | Cys | Arg | Leu | Gln | Ile | Arg | Phe | | | | | |
| | 210 | | | | | 215 | | | | | | | | | |

<210> 242
 <211> 181
 <212> PRT
 <213> Homo sapiens

<400> 242
 Met Gly Leu Ile Val Val Leu Leu Phe Pro Asn Leu Cys Met Cys Thr
 1 5 10 15
 Phe His Ala Gly Gly Phe Gln Cys Val Leu Trp Met Ala Gly Leu Lys
 20 25 30
 Arg Arg Val Pro Leu His Ser Leu Arg Tyr Phe Ile Ser Met Val Gly
 35 40 45
 Leu Phe Ser Lys Pro Gly Leu Leu Pro Trp Tyr Ala Arg Asn Pro Pro
 50 55 60
 Gly Trp Ser Gln Leu Phe Leu Gly Thr Val Cys Lys Gly Asp Phe Thr
 65 70 75 80
 Arg Val Ile Ala Thr Lys Cys Gln Lys Gly Gln Lys Ser Gln Lys Lys
 85 90 95
 Pro Ser His Leu Gly Pro Leu Asp Gly Ser Trp Gln Glu Arg Leu Ala
 100 105 110
 Asp Val Val Thr Pro Leu Trp Arg Leu Ser Tyr Glu Glu Gln Leu Lys
 115 120 125
 Val Lys Phe Ala Ala Gln Lys Lys Ile Leu Gln Arg Leu Glu Ser Tyr
 130 135 140
 Ile Gln Met Leu Asn Gly Val Ser Val Thr Thr Ala Val Pro Lys Ser
 145 150 155 160
 Glu Arg Leu Ser Cys Leu Leu His Pro Ile Ile Pro Leu Ser Cys His
 165 170 175
 Gln Trp Leu Pro Lys
 180

<210> 243
 <211> 125
 <212> PRT
 <213> Homo sapiens

<400> 243
 Met Ser Asn Thr Asn Gly Ser Ala Ile Thr Glu Phe Ile Leu Leu Gly
 1 5 10 15
 Leu Thr Asp Cys Pro Glu Leu Gln Ser Leu Leu Phe Val Leu Phe Leu
 20 25 30
 Val Val Tyr Leu Val Thr Leu Leu Gly Asn Leu Gly Met Ile Met Leu
 35 40 45
 Met Arg Leu Asp Ser Arg Leu His Thr Pro Met Tyr Phe Phe Leu Thr
 50 55 60
 Asn Leu Ala Phe Val Asp Leu Cys Tyr Thr Ser Asn Ala Thr Pro Gln
 65 70 75 80
 Met Ser Thr Asn Ile Val Ser Glu Lys Thr Ile Ser Phe Ala Gly Cys
 85 90 95
 Phe Thr Gln Cys Tyr Ile Phe Ile Ala Leu Leu Leu Thr Glu Phe Tyr
 100 105 110
 Met Leu Ala Ala Met Ala Tyr Asp Arg Tyr Val Ala Ile
 115 120 125

<210> 244
 <211> 132
 <212> PRT
 <213> Homo sapiens

<400> 244
 Met Arg Leu Leu Val Leu Ser Ser Leu Leu Cys Ile Leu Leu Leu Cys
 1 5 10 15
 Phe Ser Ile Phe Ser Thr Glu Gly Lys Arg Arg Pro Ala Lys Ala Trp
 20 25 30
 Ser Gly Arg Arg Thr Arg Leu Cys Cys His Arg Val Pro Ser Pro Asn
 35 40 45
 Ser Thr Asn Leu Lys Ala Phe Thr Ala Val Ser Cys Asn Val Gly Gly
 50 55 60
 Leu His Leu Gly Leu Gln Gly Pro Trp Glu Ser Ser Arg Thr Pro Arg
 65 70 75 80
 Pro Cys Leu Asn Cys Ala Ile Asn Phe Gln Ser Tyr His Glu Pro Thr
 85 90 95
 Ser Pro His Arg Ala Ser Val Ala Thr Met Trp Ala Ser Pro Val Gln
 100 105 110
 Thr Thr Glu His Ser Thr Met Thr Gly His Ser Tyr Lys Ser Arg Asp
 115 120 125
 His Gln Ser Cys

130

<210> 245

<211> 186

<212> PRT

<213> Homo sapiens

<400> 245

Met Ser Gly Leu Ser Arg Pro Leu Leu Leu Ala Val Gly Cys Leu Ala
 1 5 10 15

Ala Leu Cys Val Ile Thr Ala Ala Gly Asn Thr Thr Leu Ala Pro Asn
 20 25 30

Val Thr Thr Ala Ser Ser Pro Pro Pro Thr Thr Thr Thr Val Pro Val
 35 40 45

Ser Pro Thr Thr Leu Ser Pro Leu Pro Val Thr Thr Pro Ala Pro Asp
 50 55 60

Ile Cys Gly Ser Arg Asn Ser Cys Val Ser Cys Val Asp Gly Asn Ala
 65 70 75 80

Thr Cys Phe Trp Ile Glu Cys Lys Gly Lys Ser Tyr Cys Ser Asp Asn
 85 90 95

Ser Thr Ala Gly Asp Cys Lys Val Val Asn Thr Thr Gly Phe Cys Ser
 100 105 110

Ala Lys Thr Thr Thr Leu Pro Ser Thr Thr Thr Thr Ser Thr Thr Ala
 115 120 125

Thr Thr Ser Gly Thr Thr Asn Thr Thr Leu Ser Pro Thr Ile Gln Pro
 130 135 140

Thr Arg Lys Ser Thr Phe Asp Ala Ala Ser Phe Ile Gly Gly Ile Val
 145 150 155 160

Leu Val Leu Gly Val Gln Ala Val Ile Phe Phe Leu Tyr Lys Phe Cys
 165 170 175

Lys Ser Lys Glu Arg Asn Tyr His Thr Leu
 180 185

<210> 246

<211> 114

<212> PRT

<213> Homo sapiens

<400> 246

Met Leu Val Pro Ala Ala Leu Thr Gly Leu Leu Val Phe Leu Ser Gly
 1 5 10 15

Phe Ser Leu Phe Glu Ala Ser Gln Ile Ser Lys Glu Ile Cys Glu Ala
 20 25 30

His Asp Ile Leu Met Cys Pro Leu Gly Asp His Ser Arg Arg Tyr Gln
 35 40 45

Arg Leu Ser Glu Thr Cys Thr Phe Ala Lys Leu Thr His Leu Phe Asp
 50 55 60

135

Asn Asp Gly Thr Val Val Phe Ala Ile Phe Met Ala Leu Trp Ala Thr
 65 70 75 80

Val Phe Leu Glu Ile Trp Lys Arg Gln Arg Ala Arg Val Val Leu His
 85 90 95

Trp Asp Leu Tyr Val Trp Asp Glu Glu Gln Val Arg Trp Ser Trp Gln
 100 105 110

Arg Ser

<210> 247
 <211> 91
 <212> PRT
 <213> Homo sapiens

<400> 247
 Met Ser Arg Cys Thr Trp Pro Ser Phe Ser Phe Phe Leu Ser Ser Phe
 1 5 10 15

Leu Ser Phe Phe Arg Trp Ser Leu Ala Leu Ser Ala Arg Leu Glu Gly
 20 25 30

Ser Gly Val Ile Leu Ala His Cys Asn Leu Arg Leu Pro Gly Ser Ser
 35 40 45

Asp Ser Pro Ala Ser Ala Ser Gln Ser Ala Gly Ile Thr Gly Met Ser
 50 55 60

Arg Cys Ala Asp Val His Leu Val Ser Ile Ile Thr Lys Ala His Leu
 65 70 75 80

Val Ser Trp Pro Leu Gln Met Asn Ile Leu Pro
 85 90

<210> 248
 <211> 73
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (33)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (34)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (52)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 248
 Met Val Phe Pro Leu Leu Cys Val Phe Val Leu Ile Ser Ser Ser Leu
 1 5 10 15

Ala Gly Glu Glu Ala Ala Gly Leu Arg Val Gln Lys Leu Trp Pro Ala
 20 25 30

136

Xaa Xaa Leu Ser His Leu Pro Val Cys Trp Phe His Cys Ser Gly Ile
 35 40 45
 Trp Ser Glu Xaa Ile Glu Leu Lys Val Gly Trp Glu Gly His Val Leu
 50 55 60
 Pro Trp Gln Ala His Val Val Glu Phe
 65 70

<210> 249
 <211> 118
 <212> PRT
 <213> Homo sapiens

<400> 249
 Met His Cys His Cys Arg Val Trp Gly Phe Arg Trp Phe Leu Gly Asp
 1 5 10 15
 Trp Glu Leu Leu Val Cys Met Cys Trp Val His Ala Ser Gly Ser Gln
 20 25 30
 Leu Pro Gln Ala Arg Thr Gly Asn Pro Phe Pro Ser Lys Ala Ile Gly
 35 40 45
 Gly Ala Ser Leu Glu Ser Phe Ala Lys Ser Pro Arg Gln Asn Pro Arg
 50 55 60
 Val Gln Asp His Phe His Gly Ala His Val Phe Leu Phe Cys Arg Asn
 65 70 75 80
 Phe Phe Leu Thr Ser Thr His His Asn Ser Glu Gly His Val Ser Ser
 85 90 95
 Phe Leu Asp His Tyr Ser Glu Val Leu Gln Leu Tyr Ser Ser Gln Ser
 100 105 110
 Gly Leu Gly Leu Leu Gly
 115

<210> 250
 <211> 466
 <212> PRT
 <213> Homo sapiens

<400> 250
 Met Phe Gly Thr Leu Leu Leu Tyr Cys Phe Phe Leu Ala Thr Val Pro
 1 5 10 15
 Ala Leu Ala Glu Thr Gly Gly Glu Arg Gln Leu Ser Pro Glu Lys Ser
 20 25 30
 Glu Ile Trp Gly Pro Gly Leu Lys Ala Asp Val Val Leu Pro Ala Arg
 35 40 45
 Tyr Phe Tyr Ile Gln Ala Val Asp Thr Ser Gly Asn Lys Phe Thr Ser
 50 55 60
 Ser Pro Gly Glu Lys Val Phe Gln Val Lys Val Ser Ala Pro Glu Glu
 65 70 75 80
 Gln Phe Thr Arg Val Gly Val Gln Val Leu Asp Arg Lys Asp Gly Ser

137

| | | | | | | | | | | | | | | | |
|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| 85 | | | | | | | | 90 | | | | 95 | | | |
| Phe | Ile | Val | Arg 100 | Tyr | Arg | Met | Tyr | Ala 105 | Ser | Tyr | Lys | Asn | Leu 110 | Lys | Val |
| Glu | Val | Lys 115 | Phe | Gln | Gly | Gln | His 120 | Val | Ala | Lys | Ser | Pro 125 | Tyr | Ile | Leu |
| Lys | Gly 130 | Pro | Val | Tyr | His | Glu 135 | Asn | Cys | Asp | Cys | Pro 140 | Leu | Gln | Asp | Ser |
| Ala 145 | Ala | Trp | Leu | Arg | Glu 150 | Met | Asn | Cys | Pro | Glu 155 | Thr | Ile | Ala | Gln | Ile 160 |
| Gln | Arg | Asp | Leu | Ala 165 | His | Phe | Pro | Ala | Val 170 | Asp | Pro | Glu | Lys | Ile 175 | Ala |
| Val | Glu | Ile | Pro 180 | Lys | Arg | Phe | Gly | Gln 185 | Arg | Gln | Ser | Leu | Cys 190 | His | Tyr |
| Thr | Leu | Lys 195 | Asp | Asn | Lys | Val | Tyr 200 | Ile | Lys | Thr | His | Gly 205 | Glu | His | Val |
| Gly | Phe 210 | Arg | Ile | Phe | Met | Asp 215 | Ala | Ile | Leu | Leu | Ser 220 | Leu | Thr | Arg | Lys |
| Val 225 | Lys | Met | Pro | Asp | Val 230 | Glu | Leu | Phe | Val | Asn 235 | Leu | Gly | Asp | Trp | Pro 240 |
| Leu | Glu | Lys | Lys | Lys 245 | Ser | Asn | Ser | Asn | Ile 250 | His | Pro | Ile | Phe | Ser 255 | Trp |
| Cys | Gly | Ser | Thr 260 | Asp | Ser | Lys | Asp | Ile 265 | Val | Met | Pro | Thr | Tyr 270 | Asp | Leu |
| Thr | Asp | Ser 275 | Val | Leu | Glu | Thr | Met 280 | Gly | Arg | Val | Ser | Leu 285 | Asp | Met | Met |
| Ser | Val 290 | Gln | Ala | Asn | Thr | Gly 295 | Pro | Pro | Trp | Glu | Ser 300 | Lys | Asn | Ser | Thr |
| Ala 305 | Val | Trp | Arg | Gly | Arg 310 | Asp | Ser | Arg | Lys | Glu 315 | Arg | Leu | Glu | Leu | Val 320 |
| Lys | Leu | Ser | Arg | Lys 325 | His | Pro | Glu | Leu | Ile 330 | Asp | Ala | Ala | Phe | Thr 335 | Asn |
| Phe | Phe | Phe | Phe 340 | Lys | His | Asp | Glu | Asn 345 | Leu | Tyr | Gly | Pro | Ile 350 | Val | Lys |
| His | Ile | Ser 355 | Phe | Phe | Asp | Phe | Phe 360 | Lys | His | Lys | Tyr | Gln 365 | Ile | Asn | Ile |
| Asp | Gly 370 | Thr | Val | Ala | Ala | Tyr 375 | Arg | Leu | Pro | Tyr | Leu 380 | Leu | Val | Gly | Asp |
| Ser 385 | Val | Val | Leu | Lys | Gln 390 | Asp | Ser | Ile | Tyr | Tyr 395 | Glu | His | Phe | Tyr | Asn 400 |
| Glu | Leu | Gln | Pro | Trp 405 | Lys | His | Tyr | Ile | Pro 410 | Val | Lys | Ser | Asn | Leu 415 | Ser |
| Asp | Leu | Leu | Glu 420 | Lys | Leu | Lys | Trp | Ala 425 | Lys | Asp | His | Asp | Glu 430 | Glu | Ala |
| Lys | Lys | Ile | Ala | Lys | Ala | Gly | Gln | Glu | Phe | Ala | Arg | Asn | Asn | Leu | Met |

138

435 440 445
 Gly Asp Asp Ile Phe Cys Tyr Tyr Phe Lys Leu Phe Gln Thr Lys Asp
 450 455 460
 Glu Leu
 465

<210> 251
 <211> 62
 <212> PRT
 <213> Homo sapiens

<400> 251
 Met Thr Cys Gln Leu Leu Phe Asn Ser Phe Leu Leu Ser Ser Val Ser
 1 5 10 15
 Gln Ile Arg Asp Gln Ile Ala Met Arg Glu Ser Val Trp Ser Gly Ser
 20 25 30
 Ile Ser Arg Gln Lys Glu Leu Val Thr Leu Trp Ile Ile Cys Leu Trp
 35 40 45
 Phe Arg His Leu Pro Leu Val Leu Ala Val Gly Asp Gly Trp
 50 55 60

<210> 252
 <211> 306
 <212> PRT
 <213> Homo sapiens

<400> 252
 Met Gly His Arg Thr Leu Val Leu Pro Trp Val Leu Leu Thr Leu Cys
 1 5 10 15
 Val Thr Ala Gly Thr Pro Glu Val Trp Val Gln Val Arg Met Glu Ala
 20 25 30
 Thr Glu Leu Ser Ser Phe Thr Ile Arg Cys Gly Phe Leu Gly Ser Gly
 35 40 45
 Ser Ile Ser Leu Val Thr Val Ser Trp Gly Gly Pro Asp Gly Ala Gly
 50 55 60
 Gly Thr Thr Leu Ala Val Leu His Pro Glu Arg Gly Ile Arg Gln Trp
 65 70 75 80
 Ala Pro Ala Arg Gln Ala Arg Trp Glu Thr Gln Ser Ser Ile Ser Leu
 85 90 95
 Ile Leu Glu Gly Ser Gly Ala Ser Ser Pro Cys Ala Asn Thr Thr Phe
 100 105 110
 Cys Cys Lys Phe Ala Ser Phe Pro Glu Gly Ser Trp Glu Ala Cys Gly
 115 120 125
 Ser Leu Pro Pro Ser Ser Asp Pro Gly Leu Ser Ala Pro Pro Thr Pro
 130 135 140
 Ala Pro Ile Leu Arg Ala Asp Leu Ala Gly Ile Leu Gly Val Ser Gly
 145 150 155 160

Val Leu Leu Phe Gly Cys Val Tyr Leu Leu His Leu Leu Arg Arg His
 165 170 175
 Lys His Arg Pro Ala Pro Arg Leu Gln Pro Ser Arg Thr Ser Pro Gln
 180 185 190
 Ala Pro Arg Ala Arg Ala Trp Ala Pro Ser Gln Ala Ser Gln Ala Ala
 195 200 205
 Leu His Val Pro Tyr Ala Thr Ile Asn Thr Ser Cys Arg Pro Ala Thr
 210 215 220
 Leu Asp Thr Ala His Pro His Gly Gly Pro Ser Trp Trp Ala Ser Leu
 225 230 235 240
 Pro Thr His Ala Ala His Arg Pro Gln Gly Pro Ala Ala Trp Ala Ser
 245 250 255
 Thr Pro Ile Pro Ala Arg Gly Ser Phe Val Ser Val Glu Asn Gly Leu
 260 265 270
 Tyr Ala Gln Ala Gly Glu Arg Pro Pro His Thr Gly Pro Gly Leu Thr
 275 280 285
 Leu Phe Pro Asp Pro Arg Gly Pro Arg Ala Met Glu Gly Pro Leu Gly
 290 295 300
 Val Arg
 305

<210> 253
 <211> 191
 <212> PRT
 <213> Homo sapiens

<400> 253
 Met Gly Trp Ser Arg Gly Glu Gly Gln Gln Gly Trp Leu Ala Ala Ala
 1 5 10 15
 Leu Cys Gly Trp Thr Arg Leu Gly Lys Ala Glu Gly Ser Glu Gly Trp
 20 25 30
 Ala Thr Leu Glu Gly Cys Gln Val Pro Ser Leu Leu Gln Gly Asn Glu
 35 40 45
 Gly Gly Ala Ala Leu Asn Arg His Met Pro Lys Gln Gly Ile Asp Ala
 50 55 60
 Trp Ile Lys Leu Ala Thr Thr Arg Arg Ser Leu Phe Gly Ile Phe Gln
 65 70 75 80
 Ile Leu Arg His Pro Ser Cys Asp Asp Gly Val Glu Arg Gly Thr Gly
 85 90 95
 Pro Leu Glu Phe Cys Gly Leu His Arg His Ser Ala Gly Ile Trp Thr
 100 105 110
 Cys Arg Leu Val Gly Pro Ala Gly Ser Leu Leu Pro Ala Leu Leu Arg
 115 120 125
 Gly Arg Gly Gln Leu Gly Gly Arg Gly Leu Ala Glu Lys Gln Lys Asn
 130 135 140

140

Met Gly Cys Gly Ala Pro Ser Ala Ala Arg Gly Ser Asn Pro Ser Ser
 145 150 155 160

Ser Met Trp Glu Pro Ser Thr Pro Gly Ser Leu Ser Gln Pro Cys Leu
 165 170 175

Gly Pro Gly Trp Glu Asn Pro Thr Pro Gln Gly Cys Gly Glu Gly
 180 185 190

<210> 254
 <211> 146
 <212> PRT
 <213> Homo sapiens

<400> 254
 Met Arg Leu Phe Val Ser Val Thr Val Leu Val Ile Cys Leu Ala Asp
 1 5 10 15

Leu Glu Glu Glu Ser Glu Ser Trp Asp Asn Ser Glu Ser Glu Glu Glu
 20 25 30

Glu Lys Ala Pro Val Leu Pro Glu Ser Thr Glu Gly Arg Glu Leu Thr
 35 40 45

Gln Gly Pro Ala Glu Ser Ser Ser Leu Ser Gly Cys Gly Ser Trp Gln
 50 55 60

Pro Arg Lys Leu Pro Val Phe Lys Ser Leu Arg His Met Arg Gln Val
 65 70 75 80

Gly Gly Arg Gly Thr Ala His Gln Glu Leu Arg Arg Arg Ala Asn His
 85 90 95

Gly Leu Ser Leu Pro Thr Arg Leu Ala Ser Gly Pro Ser Thr Phe Lys
 100 105 110

Thr Leu Gln Glu Val Thr Asp Ser Leu Leu Gly Gly Trp Leu Arg Ala
 115 120 125

Gln Gly Val Gly Gly Ile Ser His Arg Ile Ser Ala Pro Leu Ser Val
 130 135 140

Met Thr
 145

<210> 255
 <211> 777
 <212> PRT
 <213> Homo sapiens

<400> 255
 Met Ile Leu Leu Ile Ile Leu Trp Ile Leu Arg Glu Ile Gln Ser Ile
 1 5 10 15

Tyr Ile Ile Gly Ile Phe Arg Asn Pro Phe Tyr Pro Lys Asp Val Gln
 20 25 30

Thr Val Thr Val Phe Phe Glu Lys Gln Thr Arg Leu Met Lys Ile Gly
 35 40 45

Ile Val Arg Arg Ile Leu Leu Thr Leu Val Ser Pro Phe Ala Met Ile
 50 55 60

141

| | | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
| Ala | Phe | Leu | Ser | Leu | Asp | Ser | Ser | Leu | Gln | Gly | Leu | His | Ser | Val | Ser | |
| 65 | | | | | 70 | | | | | 75 | | | | | 80 | |
| Val | Cys | Ile | Gly | Phe | Thr | Arg | Ala | Phe | Arg | Met | Val | Trp | Gln | Asn | Thr | |
| | | | | 85 | | | | | 90 | | | | | 95 | | |
| Glu | Asn | Ala | Leu | Leu | Glu | Thr | Val | Ile | Val | Ser | Thr | Val | His | Leu | Ile | |
| | | | 100 | | | | | 105 | | | | | 110 | | | |
| Ser | Ser | Thr | Asp | Ile | Trp | Trp | Asn | Arg | Ser | Leu | Asp | Thr | Gly | Leu | Arg | |
| | | 115 | | | | | 120 | | | | | 125 | | | | |
| Leu | Leu | Leu | Val | Gly | Ile | Ile | Arg | Asp | Arg | Leu | Ile | Gln | Phe | Ile | Ser | |
| | 130 | | | | | 135 | | | | | 140 | | | | | |
| Lys | Leu | Gln | Phe | Ala | Val | Thr | Val | Leu | Leu | Thr | Ser | Trp | Thr | Glu | Lys | |
| 145 | | | | | 150 | | | | | 155 | | | | | 160 | |
| Lys | Gln | Arg | Arg | Lys | Thr | Thr | Ala | Thr | Leu | Cys | Ile | Leu | Asn | Ile | Val | |
| | | | | 165 | | | | | 170 | | | | | 175 | | |
| Phe | Ser | Pro | Phe | Val | Leu | Val | Ile | Ile | Val | Phe | Ser | Thr | Leu | Leu | Ser | |
| | | | 180 | | | | | 185 | | | | | 190 | | | |
| Ser | Pro | Leu | Leu | Pro | Leu | Phe | Thr | Leu | Pro | Val | Phe | Leu | Val | Gly | Phe | |
| | | 195 | | | | | 200 | | | | | 205 | | | | |
| Pro | Arg | Pro | Ile | Gln | Ser | Trp | Pro | Gly | Ala | Ala | Gly | Thr | Thr | Ala | Cys | |
| | 210 | | | | | 215 | | | | | 220 | | | | | |
| Val | Cys | Ala | Asp | Thr | Val | Tyr | Tyr | Tyr | Gln | Met | Val | Pro | Arg | Leu | Thr | |
| 225 | | | | | 230 | | | | | 235 | | | | | 240 | |
| Ala | Val | Leu | Gln | Thr | Ala | Met | Ala | Ala | Gly | Ser | Leu | Gly | Leu | Leu | Leu | |
| | | | | 245 | | | | | 250 | | | | | 255 | | |
| Pro | Gly | Ser | His | Tyr | Leu | Gly | Arg | Phe | Gln | Asp | Arg | Leu | Met | Trp | Ile | |
| | | | 260 | | | | | 265 | | | | | 270 | | | |
| Met | Ile | Leu | Glu | Cys | Gly | Tyr | Thr | Tyr | Cys | Ser | Ile | Asn | Ile | Lys | Gly | |
| | 275 | | | | | | 280 | | | | | 285 | | | | |
| Leu | Glu | Leu | Gln | Glu | Thr | Ser | Cys | His | Thr | Ala | Glu | Ala | Arg | Arg | Val | |
| | 290 | | | | | 295 | | | | | 300 | | | | | |
| Asp | Glu | Val | Phe | Glu | Asp | Ala | Phe | Glu | Gln | Glu | Tyr | Thr | Arg | Val | Cys | |
| 305 | | | | | 310 | | | | | 315 | | | | | 320 | |
| Ser | Leu | Asn | Glu | His | Phe | Gly | Asn | Val | Leu | Thr | Pro | Cys | Thr | Val | Leu | |
| | | | | 325 | | | | | 330 | | | | | 335 | | |
| Pro | Val | Lys | Leu | Tyr | Ser | Asp | Ala | Arg | Asn | Val | Leu | Ser | Gly | Ile | Ile | |
| | | 340 | | | | | 345 | | | | | | 350 | | | |
| Asp | Ser | His | Glu | Asn | Leu | Lys | Asp | Phe | Lys | Gly | Asp | Leu | Ile | Lys | Val | |
| | | 355 | | | | | 360 | | | | | 365 | | | | |
| Leu | Val | Trp | Ile | Leu | Val | Gln | Tyr | Cys | Ser | Lys | Arg | Pro | Gly | Met | Lys | |
| | 370 | | | | | 375 | | | | | 380 | | | | | |
| Glu | Asn | Val | His | Asn | Thr | Glu | Asn | Lys | Gly | Lys | Ala | Pro | Leu | Met | Leu | |
| 385 | | | | | 390 | | | | | 395 | | | | | 400 | |
| Pro | Ala | Leu | Asn | Thr | Leu | Pro | Pro | Pro | Lys | Ser | Pro | Glu | Asp | Ile | Asp | |
| | | | | 405 | | | | | 410 | | | | | 415 | | |

Ser Leu Asn Ser Glu Thr Phe Asn Asp Trp Ser Asp Asp Asn Ile Phe
 420 425 430
 Asp Asp Glu Pro Thr Ile Lys Lys Val Ile Glu Glu Lys His Gln Leu
 435 440 445
 Lys Asp Leu Pro Gly Thr Asn Leu Phe Ile Pro Gly Ser Val Glu Ser
 450 455 460
 Gln Arg Val Gly Asp His Ser Thr Gly Thr Val Pro Glu Asn Asp Leu
 465 470 475 480
 Tyr Lys Ala Val Leu Leu Gly Tyr Pro Ala Val Asp Lys Gly Lys Gln
 485 490 495
 Glu Asp Met Pro Tyr Ile Pro Leu Met Glu Phe Ser Cys Ser His Ser
 500 505 510
 His Leu Val Cys Leu Pro Ala Glu Trp Arg Thr Ser Cys Met Pro Ser
 515 520 525
 Ser Lys Met Lys Glu Met Ser Ser Leu Phe Pro Glu Asp Trp Tyr Gln
 530 535 540
 Phe Val Leu Arg Gln Leu Glu Cys Tyr His Ser Glu Glu Lys Ala Ser
 545 550 555 560
 Asn Val Leu Glu Glu Ile Ala Lys Asp Lys Val Leu Lys Asp Phe Tyr
 565 570 575
 Val His Thr Val Met Thr Cys Tyr Phe Ser Leu Phe Gly Ile Asp Asn
 580 585 590
 Met Ala Pro Ser Pro Gly His Ile Leu Arg Val Tyr Gly Gly Val Leu
 595 600 605
 Pro Trp Ser Val Ala Leu Asp Trp Leu Thr Glu Lys Pro Glu Leu Phe
 610 615 620
 Gln Leu Ala Leu Lys Ala Phe Arg Tyr Thr Leu Lys Leu Met Ile Asp
 625 630 635 640
 Lys Ala Ser Leu Gly Pro Ile Glu Asp Phe Arg Glu Leu Ile Lys Tyr
 645 650 655
 Leu Glu Glu Tyr Glu Arg Asp Trp Tyr Ile Gly Leu Val Ser Asp Glu
 660 665 670
 Lys Trp Lys Glu Ala Ile Leu Gln Glu Lys Pro Tyr Leu Phe Ser Leu
 675 680 685
 Gly Tyr Asp Ser Asn Met Gly Ile Tyr Thr Gly Arg Val Leu Ser Leu
 690 695 700
 Gln Glu Leu Leu Ile Gln Val Gly Lys Leu Asn Pro Glu Ala Val Arg
 705 710 715 720
 Gly Gln Trp Ala Asn Leu Ser Trp Glu Leu Leu Tyr Ala Thr Asn Asp
 725 730 735
 Asp Glu Glu Arg Tyr Ser Ile Gln Ala His Pro Leu Leu Leu Arg Asn
 740 745 750
 Leu Thr Val Gln Ala Ala Glu Pro Pro Leu Gly Tyr Pro Ile Tyr Ser
 755 760 765

143

Ser Lys Pro Leu His Ile His Leu Tyr
 770 775

<210> 256
 <211> 217
 <212> PRT
 <213> Homo sapiens

<400> 256
 Met Glu Met Ala Ser Ser Ala Gly Ser Trp Leu Ser Gly Cys Leu Ile
 1 5 10 15
 Pro Leu Val Phe Leu Arg Leu Ser Val His Val Ser Gly His Ala Gly
 20 25 30
 Asp Ala Gly Lys Phe His Val Ala Leu Leu Gly Gly Thr Ala Glu Leu
 35 40 45
 Leu Cys Pro Leu Ser Leu Trp Pro Gly Thr Val Pro Lys Glu Val Arg
 50 55 60
 Trp Leu Arg Ser Pro Phe Pro Gln Arg Ser Gln Ala Val His Ile Phe
 65 70 75 80
 Arg Asp Gly Lys Asp Gln Asp Glu Asp Leu Met Pro Glu Tyr Lys Gly
 85 90 95
 Arg Thr Val Leu Val Arg Asp Ala Gln Glu Gly Ser Val Thr Leu Gln
 100 105 110
 Ile Leu Asp Val Arg Leu Glu Asp Gln Gly Ser Tyr Arg Cys Leu Ile
 115 120 125
 Gln Val Gly Asn Leu Ser Lys Glu Asp Thr Val Ile Leu Gln Val Ala
 130 135 140
 Ala Pro Ser Val Gly Ser Leu Ser Pro Ser Ala Val Ala Leu Ala Val
 145 150 155 160
 Ile Leu Pro Val Leu Val Leu Leu Ile Met Val Cys Leu Cys Leu Ile
 165 170 175
 Trp Lys Gln Arg Arg Ala Lys Glu Lys Leu Leu Tyr Glu His Val Thr
 180 185 190
 Glu Thr Ile Phe Phe Gln Thr Met Leu Lys Lys Lys Glu Asn Ser Ile
 195 200 205
 Lys Leu Ser Arg Asn Ser Gly Val Asn
 210 215

<210> 257
 <211> 93
 <212> PRT
 <213> Homo sapiens

<400> 257
 Met Ser His Cys Cys Ser Leu Arg Val Asp Phe Ser Val Pro Leu Cys
 1 5 10 15
 Met Leu Leu Ser Pro Leu Leu Gly Met Ser Phe Ser Ala Cys Gln Thr

144

| | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|
| | 20 | | 25 | | 30 | |
| Pro | Ser | Lys | Ser | Ser | Ser | Asp |
| | | 35 | | | | 40 |
| Val | Thr | Phe | Ser | Leu | Ser | Thr |
| | | | | 45 | | Pro |
| Asp | | | | | | |
| Pro | Thr | Pro | Gln | Ile | Asp | Leu |
| | 50 | | | | 55 | |
| Val | Gln | Pro | Ser | Ser | Gly | Phe |
| | | | | 60 | | Pro |
| Gln | | | | | | |
| His | Ser | Val | Gln | Phe | Glu | Arg |
| | 65 | | | | 70 | |
| Ser | Phe | Ile | Ile | Val | Ile | Ile |
| | | | 75 | | | Thr |
| Phe | | | | | | 80 |
| | | | | | | |
| Phe | Lys | Asn | Asn | Phe | Ile | Phe |
| | | | | 85 | | |
| Ile | Phe | Ile | Asn | Leu | Ile | Arg |
| | | | | 90 | | Leu |

<210> 258
 <211> 122
 <212> PRT
 <213> Homo sapiens

<400> 258
 Met Leu His Ser Leu Ala Leu Ala Glu Phe Cys Arg Asp Trp Gln His
 1 5 10 15
 Cys Val Pro Ala Cys Ser Pro Thr Val Ala Val Leu Phe Pro Arg Val
 20 25 30
 Gln Arg Arg Phe Phe Leu Cys Ala Leu Trp Leu Leu Arg Ala His Gly
 35 40 45
 Gly Gly Leu Gly Ser Ala Ile Gln Asp Cys Leu Phe Tyr Pro Leu His
 50 55 60
 Cys Leu Phe Gln Gln Tyr Glu Gly Thr Val Ile Ala His Met Ile Phe
 65 70 75 80
 Gly Ser Tyr Glu Gly Ala Phe Cys Val Gly Gly Cys Gln Ile Trp Cys
 85 90 95
 Ser Cys Arg Glu Asp Asn Arg Trp Arg Leu Leu Phe Gly His Ile Ala
 100 105 110
 Leu Pro Pro Ile Pro Ala Cys Phe Tyr Phe
 115 120

<210> 259
 <211> 113
 <212> PRT
 <213> Homo sapiens

<400> 259
 Met Gly Ala Ala Trp Pro Arg Arg Ala Arg Ser Trp Trp Ile Arg Thr
 1 5 10 15
 Ser Thr Ala Ser Ser Pro Ser Pro Ser Ser Ile Thr Leu Leu Trp
 20 25 30
 Thr Pro Cys Met Trp Ala Glu Ser Trp Ala Cys Cys Ser Ser Pro Thr
 35 40 45
 Tyr Thr Arg Thr Gly Lys Cys Ser Thr Asn Arg Thr Pro Arg Trp Pro
 50 55 60

145

Pro Ala Leu Thr Ser Met Pro Arg Thr Ser Thr Phe Gln Gln Trp Leu
 65 70 75 80
 Ser Ser Pro Thr Phe Trp Trp Leu Val Leu Arg Trp Gly Pro Arg Ile
 85 90 95
 Gly Ser Pro Gln Thr Ser Trp Gly Cys Lys Arg Ala Gln Pro Trp Pro
 100 105 110
 Gly

<210> 260
 <211> 215
 <212> PRT
 <213> Homo sapiens

<400> 260
 Met Asn Lys Arg Ala Lys Phe Glu Leu Arg Lys Pro Leu Val Leu Trp
 1 5 10 15
 Ser Leu Thr Leu Ala Val Phe Ser Ile Phe Gly Ala Leu Arg Thr Gly
 20 25 30
 Ala Tyr Met Val Tyr Ile Leu Met Thr Lys Gly Leu Lys Gln Ser Val
 35 40 45
 Cys Asp Gln Gly Phe Tyr Asn Gly Pro Val Ser Lys Phe Trp Ala Tyr
 50 55 60
 Ala Phe Val Leu Ser Lys Ala Pro Glu Leu Gly Asp Thr Ile Phe Ile
 65 70 75 80
 Ile Leu Arg Lys Gln Lys Leu Ile Phe Leu His Trp Tyr His His Ile
 85 90 95
 Thr Val Leu Leu Tyr Ser Trp Tyr Ser Tyr Lys Asp Met Val Ala Gly
 100 105 110
 Gly Gly Trp Phe Met Thr Met Asn Tyr Gly Val His Ala Val Met Tyr
 115 120 125
 Ser Tyr Tyr Ala Leu Arg Ala Ala Gly Phe Arg Val Ser Arg Lys Phe
 130 135 140
 Ala Met Phe Ile Thr Leu Ser Gln Ile Thr Gln Met Leu Met Gly Cys
 145 150 155 160
 Val Val Asn Tyr Leu Val Phe Cys Trp Met Gln His Asp Gln Cys His
 165 170 175
 Ser His Phe Gln Asn Ile Phe Trp Ser Ser Leu Met Tyr Leu Ser Tyr
 180 185 190
 Leu Val Leu Phe Cys His Phe Phe Glu Ala Tyr Ile Gly Lys Met
 195 200 205
 Arg Lys Thr Thr Lys Ala Glu
 210 215

<210> 261
 <211> 84

146

<212> PRT

<213> Homo sapiens

<400> 261

```

Met Gly Asp Lys Glu Ser Ser Ser Ser Lys Pro Ser Leu Ala Gly Trp
 1          5          10          15
Val Pro Leu Leu Leu Gly Gly Ala Phe Ser Cys Thr Pro Leu Pro Pro
          20          25          30
Arg Gly Glu Ser Gln Gln Pro Asn Gln Thr Ala Gln Val Val His Leu
          35          40          45
Met Glu Thr Thr Gly Leu Lys His Val Leu Tyr Ser Pro Val Tyr Phe
          50          55          60
Cys Cys Tyr Phe Glu Ala Trp Lys Phe Leu Phe Gly Gly Ser Trp Gly
 65          70          75          80
Tyr Ser Ser Gly

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<210> 262

<211> 116

<212> PRT

<213> Homo sapiens

<400> 262

```

Met Ala Leu Asp Ile Ser Leu Phe Tyr Leu Phe Tyr Phe Phe Phe Phe
 1          5          10          15
Leu Arg Trp Asn Phe Ser Leu Ile Ala Gln Ala Gly Val Gln Trp His
          20          25          30
Asp Leu Gly Ser Pro Gln Pro Pro Pro Gly Leu Lys Arg Phe Ser
          35          40          45
Phe Leu Gly Leu Pro Ser Ser Trp Asp Tyr Arg His Ala Pro Pro Cys
          50          55          60
Pro Ala Asn Phe Val Phe Leu Val Glu Met Gly Phe Leu His Val Gly
          65          70          75          80
Gln Ala Gly Leu Glu Leu Pro Thr Ser Gly Gly Pro Pro Ala Trp Ala
          85          90          95
Ser Gln Ser Ala Gly Ile Thr Gly Val Ser His Arg Ala Trp Pro Glu
          100          105          110
Asn Ser His Phe
          115

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<210> 263

<211> 139

<212> PRT

<213> Homo sapiens

<400> 263

```

Met Leu Ala Met Leu Leu Cys Met Leu Val Ser Val Phe Ile Leu Gly
 1          5          10          15
Val Pro Tyr Arg Gly Ser Leu Leu Ile Leu Phe Phe Ile Ser Ser Leu

```

147

20 25 30
 Phe Leu Leu Ser Thr Leu Gly Met Gly Leu Leu Ile Ser Thr Ile Thr
 35 40 45
 Arg Asn Gln Phe Asn Ala Ala Gln Val Ala Leu Asn Ala Ala Phe Leu
 50 55 60
 Pro Ser Ile Met Leu Ser Gly Phe Ile Phe Gln Ile Asp Ser Met Pro
 65 70 75 80
 Ala Val Ile Arg Ala Val Thr Tyr Ile Ile Pro Ala Arg Tyr Phe Val
 85 90 95
 Ser Thr Leu Gln Ser Leu Phe Leu Ala Gly Asn Ile Pro Val Val Leu
 100 105 110
 Val Val Asn Val Leu Phe Leu Ile Ala Ser Ala Val Met Phe Ile Gly
 115 120 125
 Leu Thr Trp Leu Lys Thr Lys Arg Arg Leu Asp
 130 135

<210> 264
 <211> 82
 <212> PRT
 <213> Homo sapiens

<400> 264
 Met Gly Trp Gln Leu Arg Ala Leu Ser Ala Val Gly Leu Trp Phe Thr
 1 5 10 15
 Ala Gly Asp Ser His Leu Ser Val Gln Val Cys Gly Gly Gly Pro Ala
 20 25 30
 Leu Thr Leu Trp His Leu Arg Ser Ser Thr Pro Thr Thr Ile Phe Pro
 35 40 45
 Ile Arg Ala Pro Gln Lys His Val Thr Phe Tyr Gln Asp Leu Val Arg
 50 55 60
 Pro Cys Val Ser Leu Leu Pro Pro Pro Leu Thr Leu Pro Phe Ser Pro
 65 70 75 80
 Asp Pro

<210> 265
 <211> 59
 <212> PRT
 <213> Homo sapiens

<400> 265
 Met Leu Cys His Ala Trp Leu Leu Leu Met Tyr Leu Phe Leu Glu Met
 1 5 10 15
 Arg Ser His Cys Val Ala Gln Thr Gly Leu Glu Leu Leu Ala Ser Ser
 20 25 30
 His Pro Pro Phe Ser Ala Ser Thr Val Ala Gly Ile Ser Gly Thr Cys
 35 40 45

148

His Cys Ala Leu Leu Ile Pro Phe Lys Ile Arg
 50 55

<210> 266
 <211> 31
 <212> PRT
 <213> Homo sapiens

<400> 266
 Met Ile His Leu Phe Leu Leu Pro Cys Pro Asn Cys Val Phe Leu Leu
 1 5 10 15
 Leu His Leu Phe Phe Gln Gln Cys Ala Ala Ser Trp Thr Thr Ser
 20 25 30

<210> 267
 <211> 87
 <212> PRT
 <213> Homo sapiens

<400> 267
 Met Thr Leu Leu Leu Thr Leu Glu Val Asp Ser Gly Thr Gln Gln Arg
 1 5 10 15
 Ala Gly Val Gly Ser Gln Gly Gln Ala Val Leu Pro Gly Leu Thr Cys
 20 25 30
 Phe Leu Leu Thr Phe Leu Leu Ala Ala Ser Val Tyr Ile Thr Gln Ser
 35 40 45
 Ala Trp Asp Asn Val Glu Val Ala Glu Val Thr Gly Tyr Phe Met Phe
 50 55 60
 Leu His Gly Ile Phe Leu Phe Leu Ile Gly Arg Arg Arg Gln Lys Leu
 65 70 75 80
 Glu Glu Met Gly Leu Leu Ser
 85

<210> 268
 <211> 73
 <212> PRT
 <213> Homo sapiens

<400> 268
 Met Tyr Pro Val Tyr Thr Thr Ser Asp Phe Cys Ser Gly Thr Phe Val
 1 5 10 15
 Leu Ile Phe Ala Trp Leu Thr Leu Ser Glu Leu Val Arg Val Leu His
 20 25 30
 Arg Lys Ile Ile Asn Trp Phe Phe Ile Phe Leu Arg Arg Phe Tyr Tyr
 35 40 45
 Gly Glu Leu Ala Tyr Ala Asn Met Glu Thr Thr Met Cys His Leu Gln
 50 55 60
 Ala Gly Asp Pro Arg Gln Leu Val Val
 65 70

149

<210> 269
 <211> 81
 <212> PRT
 <213> Homo sapiens

<400> 269
 Met Tyr Ser Pro Ser Leu Tyr Leu Leu Pro Ser Leu Pro Ser Leu Leu
 1 5 10 15
 Gln Leu Ser Leu Ser Arg Ser Pro Arg Phe Asn Lys Gly Leu Gln Arg
 20 25 30
 Ala Met Glu Lys Thr Met Lys Gly Ser Thr Ile Lys Ile Leu Leu Tyr
 35 40 45
 Phe Phe His His Ile Tyr Ala Ser Leu His Thr Phe Ile Pro Leu Pro
 50 55 60
 Asn Pro Ser Ile Phe Leu Cys Ile Ser Lys Tyr Ile Ala Asp Ile Ser
 65 70 75 80
 Thr

<210> 270
 <211> 52
 <212> PRT
 <213> Homo sapiens

<400> 270
 Met Ser Lys Lys Ser Val Ser Tyr Lys Ile Arg Tyr Phe Ser Gln Ala
 1 5 10 15
 Trp Gln Leu Met Pro Val Ile Leu Val Leu Trp Glu Ala Glu Ala Gly
 20 25 30
 Gly Ser Leu Glu Ala Arg Gln Asp His Ile Val Arg Leu Cys Leu Cys
 35 40 45
 Lys Lys Lys Lys
 50

<210> 271
 <211> 83
 <212> PRT
 <213> Homo sapiens

<400> 271
 Met Leu Cys Ser Ser Phe Leu Pro Leu Ser Thr Ala Ala Ile Trp Ala
 1 5 10 15
 Ala Leu Phe Ser Gly Met Gly Ala Val Arg His Ser Pro Ser Glu Gly
 20 25 30
 Lys Arg Ser Leu Lys Ser Ser Arg Cys Leu His Phe Trp Pro Leu Pro
 35 40 45
 Thr Gly Cys Ser Ser Pro Pro Pro Cys Asn Val Thr Thr Lys Asn
 50 55 60

150

Val Ser Arg Cys Cys Gln Lys Ser Ser Arg Asp Gly Arg Val Arg Leu
 65 70 75 80

Pro Pro Arg

<210> 272
 <211> 84
 <212> PRT
 <213> Homo sapiens

<400> 272
 Met Gly Leu Arg Leu Pro Pro Pro Leu Cys Trp Phe Leu Cys Leu Thr
 1 5 10 15
 Ser Thr Gly Gln Val Pro Met Ala Gln Ala Arg Ala Gly Val Gln Gly
 20 25 30
 Pro Met Asp Gly Arg Met Pro Ser Asn Gly Cys Leu Pro Val Ser Pro
 35 40 45
 Arg Thr Pro Tyr Gly Met Pro Tyr Leu Gly Ala Leu Trp Pro Cys Trp
 50 55 60
 Pro Cys Ser Trp Gln Gly Arg Ser Thr Ser Arg His Pro Cys Gln Gln
 65 70 75 80
 Asp Leu Ser Gly

<210> 273
 <211> 230
 <212> PRT
 <213> Homo sapiens

<400> 273
 Met Asp Val Gly Pro Ser Ser Leu Pro His Leu Gly Leu Lys Leu Leu
 1 5 10 15
 Leu Leu Leu Leu Leu Leu Pro Leu Arg Gly Gln Ala Asn Thr Gly Cys
 20 25 30
 Tyr Gly Ile Pro Gly Met Pro Gly Leu Pro Gly Ala Pro Gly Lys Asp
 35 40 45
 Gly Tyr Asp Gly Leu Pro Gly Pro Lys Gly Glu Pro Gly Ile Pro Ala
 50 55 60
 Ile Pro Gly Ile Arg Gly Pro Lys Gly Gln Lys Gly Glu Pro Gly Leu
 65 70 75 80
 Pro Gly His Pro Gly Lys Asn Gly Pro Met Gly Glu Pro Gly Glu Glu
 85 90 95
 Gly Arg Tyr Lys Gln Lys Phe Gln Ser Val Phe Thr Val Thr Arg Gln
 100 105 110
 Thr His Gln Pro Pro Ala Pro Asn Ser Leu Ile Arg Phe Asn Ala Val
 115 120 125
 Leu Thr Asn Pro Gln Gly Asp Tyr Asp Thr Ser Thr Gly Lys Phe Thr
 130 135 140

151

Cys Lys Val Pro Gly Leu Tyr Tyr Phe Val Tyr His Ala Ser His Thr
 145 150 155 160
 Ala Asn Leu Cys Val Leu Leu Tyr Arg Ser Gly Val Lys Val Val Thr
 165 170 175
 Phe Cys Gly His Thr Ser Lys Thr Asn Gln Val Asn Ser Gly Gly Val
 180 185 190
 Leu Leu Arg Leu Gln Val Gly Glu Glu Val Trp Leu Ala Val Asn Asp
 195 200 205
 Tyr Tyr Asp Met Val Gly Ile Gln Gly Ser Asp Ser Val Phe Ser Gly
 210 215 220
 Phe Leu Leu Phe Pro Asp
 225 230

<210> 274
 <211> 83
 <212> PRT
 <213> Homo sapiens

<400> 274
 Met Cys Ala Met Ala Pro Leu Trp Ser Pro Leu Cys Pro Ser Ile Cys
 1 5 10 15
 Met Cys Ser Val Ser Leu Ala Cys Val Arg Val Arg Val Ser Ala Tyr
 20 25 30
 Ala Ser Thr His Trp Ala Leu Gly Cys Ser Gln Gly Lys Phe Asp Leu
 35 40 45
 Glu Arg Leu Ser Ser Pro Trp Asn Gln Asp Phe Leu Ser Pro Pro His
 50 55 60
 Pro Gly Pro Val Pro Pro Trp Leu Ser Gly Tyr Trp Gly Met Glu Thr
 65 70 75 80
 Leu Gly Glu

<210> 275
 <211> 91
 <212> PRT
 <213> Homo sapiens

<400> 275
 Met Arg Pro Gln Glu Leu Pro Arg Leu Ala Phe Pro Leu Leu Leu Leu
 1 5 10 15
 Leu Leu Leu Leu Leu Pro Pro Pro Pro Cys Pro Ala His Ser Ala Thr
 20 25 30
 Arg Phe Asp Pro Thr Trp Glu Ser Leu Asp Ala Arg Gln Leu Pro Ala
 35 40 45
 Trp Phe Asp Gln Ala Lys Phe Gly Ile Phe Ile His Trp Gly Val Phe
 50 55 60
 Ser Val Pro Ser Phe Gly Ser Glu Trp Phe Trp Leu Tyr Leu Val Gly

152

| | | | | | | |
|---------------------|-------------------------|----|----|----|--|----|
| 65 | | 70 | | 75 | | 80 |
| Val Arg Ile Phe Val | Glu Leu Glu Cys His Arg | | | | | |
| | 85 | | 90 | | | |

<210> 276
 <211> 336
 <212> PRT
 <213> Homo sapiens

<400> 276
 Met Leu Glu Thr Gly Leu Phe Phe Leu Leu Ser Trp Ser Ala Phe Leu
 1 5 10 15
 Ser Ala Glu Ala Ala Gly Leu Thr Gly Ile Val Ala Val Leu Phe Cys
 20 25 30
 Gly Val Thr Gln Ala His Tyr Thr Tyr Asn Asn Leu Ser Ser Asp Ser
 35 40 45
 Lys Ile Arg Thr Lys Gln Leu Phe Glu Phe Met Asn Phe Leu Ala Glu
 50 55 60
 Asn Val Ile Phe Cys Tyr Met Gly Leu Ala Leu Phe Thr Phe Gln Asn
 65 70 75 80
 His Ile Phe Asn Ala Leu Phe Ile Leu Gly Ala Phe Leu Ala Ile Phe
 85 90 95
 Val Ala Arg Ala Cys Asn Ile Tyr Pro Leu Ser Phe Leu Leu Asn Leu
 100 105 110
 Gly Arg Lys Gln Lys Ile Pro Trp Asn Phe Gln His Met Met Met Phe
 115 120 125
 Ser Gly Leu Arg Gly Ala Ile Ala Phe Ala Leu Ala Ile Arg Asn Thr
 130 135 140
 Glu Ser Gln Pro Lys Gln Met Met Phe Thr Thr Thr Leu Leu Leu Val
 145 150 155 160
 Phe Phe Thr Val Trp Val Phe Gly Gly Gly Thr Thr Pro Met Leu Thr
 165 170 175
 Trp Leu Gln Ile Arg Val Gly Val Asp Leu Asp Glu Asn Leu Lys Glu
 180 185 190
 Asp Pro Ser Ser Gln His Gln Glu Ala Asn Asn Leu Asp Lys Asn Met
 195 200 205
 Thr Lys Ala Glu Ser Ala Arg Leu Phe Arg Met Trp Tyr Ser Phe Asp
 210 215 220
 His Lys Tyr Leu Lys Pro Ile Leu Thr His Ser Gly Pro Pro Leu Thr
 225 230 235 240
 Thr Thr Leu Pro Glu Trp Cys Gly Pro Ile Ser Arg Leu Leu Thr Ser
 245 250 255
 Pro Gln Ala Tyr Gly Glu Gln Leu Lys Glu Asp Asp Val Glu Cys Ile
 260 265 270
 Val Asn Gln Asp Glu Leu Ala Ile Asn Tyr Gln Glu Gln Ala Ser Ser
 275 280 285

153

Pro Cys Ser Pro Pro Ala Arg Leu Gly Leu Asp Gln Lys Ala Ser Pro
 290 295 300
 Gln Thr Pro Gly Lys Glu Asn Ile Tyr Glu Gly Asp Leu Gly Leu Gly
 305 310 315 320
 Gly Tyr Glu Leu Lys Leu Glu Gln Thr Leu Gly Gln Ser Gln Leu Asn
 325 330 335

<210> 277
 <211> 106
 <212> PRT
 <213> Homo sapiens

<400> 277
 Met Gln Trp Leu Leu Ile Thr Pro Arg Leu Phe Tyr Phe Pro Leu Leu
 1 5 10 15
 Leu Leu Trp Leu Val Ser Val Lys Phe Leu Phe Ile Phe Ile Phe Gly
 20 25 30
 Asp Gly Gln Gly Leu Ala Pro Ser Leu Arg Pro Glu Cys Ser Gly Ala
 35 40 45
 Ile Met Ala His His Ser Leu Asp Phe Gln Gly Leu Ser Tyr Pro Pro
 50 55 60
 Thr Leu Ala Ser Ala Gly Ala Gly Thr Thr Gly Met His His His Ala
 65 70 75 80
 Gln Leu Ile Phe Lys Phe Phe Tyr Arg Asp Gly Val Ser Leu Cys Gly
 85 90 95
 Leu Gly Trp Ser Gln Thr Pro Gly His Lys
 100 105

<210> 278
 <211> 131
 <212> PRT
 <213> Homo sapiens

<400> 278
 Met Gly Ala Ser Leu Cys Leu Thr Gln Leu Leu Leu Leu Gly Lys
 1 5 10 15
 Gly Gly Leu Gly Gln Ala Ser Ile Pro Leu Val Lys Thr Pro Ala Gly
 20 25 30
 His Gln Ala Phe Trp Thr Arg Thr His Thr His Thr His Thr His Thr
 35 40 45
 His Thr Lys Leu His Ser Arg Pro Ala Ala Val Thr Cys His Gln Glu
 50 55 60
 Ser Pro Gln Leu Arg Pro Pro Pro Ile Leu Ser Tyr Glu Lys Pro Leu
 65 70 75 80
 Leu Trp Gly Arg Arg Leu Glu Lys Val Gly Cys Gly Gly Gln Glu Gly

154

| | | | | | |
|-------------|-------------------------|---------------------|-------------|--|----|
| | 85 | | 90 | | 95 |
| Pro Cys Arg | Ala Gly Gly Trp Val | Trp Leu Ser Arg Cys | Phe Pro Glu | | |
| | 100 | 105 | 110 | | |
| Gly Ser Ala | Gly Ile Arg Gly Ser Cys | Gly Arg Glu Arg | Ala Pro Ala | | |
| | 115 | 120 | 125 | | |
| Ser Trp Leu | | | | | |
| | 130 | | | | |

<210> 279
 <211> 81
 <212> PRT
 <213> Homo sapiens

<400> 279
 Met Cys Val His Thr Cys Val Cys Met Cys Val His Thr Cys Val Cys
 1 5 10 15
 Val His Ala Cys Val Trp Ala His Val Cys Met Cys Val Cys Glu Cys
 20 25 30
 Val Cys Trp Gly Gly Gly Met Ala Leu Gly Lys Val Cys Pro Gly Trp
 35 40 45
 Lys Pro His Ser Leu Pro Ser Ala Trp Arg Trp Ala Cys Ala Trp Arg
 50 55 60
 Pro Ile Ala Arg Arg Leu Arg Pro Thr Gly Ala Thr Ser Thr Val Pro
 65 70 75 80
 Leu

<210> 280
 <211> 108
 <212> PRT
 <213> Homo sapiens

<400> 280
 Met His Pro Pro Pro Gly Val Trp Leu Leu His Leu His Thr Pro Leu
 1 5 10 15
 Arg Gly Phe Cys Leu Pro Leu Pro Leu Arg Ser Gln Glu Ala Val Pro
 20 25 30
 Gly Arg Gly Arg Arg His Leu Ser Pro Gln Leu Leu Thr Pro His Pro
 35 40 45
 Leu Thr Ser Ser Pro Phe Val Lys Tyr Thr Gln Asp Glu Thr Cys Thr
 50 55 60
 Gln Trp Leu Thr Ala Ala Arg Phe Val Thr Ala Arg Gly Gly Glu His
 65 70 75 80
 Arg Thr Pro Ser Glu Gly Glu Gly Ile Ser Thr Ala Pro Pro Pro Cys
 85 90 95
 Trp Asn Glu Thr Gln Pro Gln Gly Gly Ala Lys Leu
 100 105

155

<210> 281
 <211> 49
 <212> PRT
 <213> Homo sapiens

<400> 281
 Met Ser Cys Thr Leu Leu Ile Cys Thr Val Val Leu Gly Val Thr Thr
 1 5 10 15
 Pro Ala Ile Gly Pro Ala Ala Pro Ser Leu Leu Ala Thr Pro Pro Gln
 20 25 30
 Ala Ala Ala Ala Thr Met Gln Pro Arg Leu Gly Arg Ala Ala Gly Ala
 35 40 45
 Ala

<210> 282
 <211> 187
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (1)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 282
 Xaa Ala Arg Asp Leu Leu Gln Ala Leu Arg His Pro Lys Ala Val Ala
 1 5 10 15
 Phe Gly Glu Met Gly Leu Asp Tyr Ser Tyr Lys Cys Thr Thr Pro Val
 20 25 30
 Pro Glu Gln His Lys Val Phe Glu Arg Gln Leu Gln Leu Ala Val Ser
 35 40 45
 Leu Lys Lys Pro Leu Val Ile His Cys Arg Glu Ala Asp Glu Asp Leu
 50 55 60
 Leu Glu Ile Met Lys Lys Phe Val Pro Pro Asp Tyr Lys Ile His Arg
 65 70 75 80
 His Cys Phe Thr Gly Ser Tyr Pro Val Ile Glu Pro Leu Leu Lys Tyr
 85 90 95
 Phe Pro Asn Met Ser Val Gly Phe Thr Ala Val Leu Thr Tyr Ser Ser
 100 105 110
 Ala Trp Glu Ala Arg Glu Ala Leu Arg Gln Ile Pro Leu Glu Arg Ile
 115 120 125
 Ile Val Glu Thr Asp Ala Pro Tyr Phe Leu Pro Arg Gln Val Pro Lys
 130 135 140
 Ser Leu Cys Gln Tyr Ala His Pro Gly Leu Ala Leu His Thr Val Arg
 145 150 155 160
 Glu Ile Ala Arg Val Lys Asp Gln Pro Leu Ser Leu Thr Leu Ala Ala
 165 170 175

156

Leu Arg Glu Asn Thr Ser Arg Leu Tyr Ser Leu
 180 185

<210> 283

<211> 95

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (80)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 283

Met Val Pro Cys Arg Lys Thr Leu Leu Phe Leu Trp Val Gly Ser Leu
 1 5 10 15

Cys Arg Asp Val Gly Ser Trp Ser Gly Trp Pro Phe Gly Leu Ser Thr
 20 25 30

Ala Thr Gln Pro Arg Leu Arg Leu Gly Lys Gln Thr Gly Ala Gly Gln
 35 40 45

Ala Arg Arg Ala Cys Arg Thr Val Ile Leu Arg Cys Gly Ser Cys Cys
 50 55 60

Arg Gly Arg Arg Thr Gly Ser Val Val Ala Trp Ser Ser Leu Pro Xaa
 65 70 75 80

Arg Thr Ser Ala Ala Glu Leu Arg Trp Arg Pro Trp Gly Pro Val
 85 90 95

<210> 284

<211> 175

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (5)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 284

Met Ala Thr Pro Xaa Gly Leu Gly Ala Leu Leu Leu Leu Leu Leu
 1 5 10 15

Pro Thr Ser Gly Gln Glu Lys Pro Thr Glu Gly Pro Arg Asn Thr Cys
 20 25 30

Leu Gly Ser Asn Asn Met Tyr Asp Ile Phe Asn Leu Asn Asp Lys Ala
 35 40 45

Leu Cys Phe Thr Lys Cys Arg Gln Ser Gly Ser Asp Ser Cys Asn Val
 50 55 60

Glu Asn Leu Gln Arg Tyr Trp Leu Asn Tyr Glu Ala His Leu Met Lys
 65 70 75 80

Glu Gly Leu Thr Gln Lys Val Asn Thr Pro Phe Leu Lys Ala Leu Val
 85 90 95

Gln Asn Leu Ser Thr Asn Thr Ala Glu Asp Phe Tyr Phe Ser Leu Glu

157

| | | |
|---|-----|-----|
| 100 | 105 | 110 |
| Pro Ser Gln Val Pro Arg Gln Val Met Lys Asp Glu Asp Lys Pro Pro | | |
| 115 | 120 | 125 |
| Asp Arg Val Arg Leu Pro Lys Ser Leu Phe Arg Ser Leu Pro Gly Asn | | |
| 130 | 135 | 140 |
| Arg Ser Val Val Arg Leu Ala Val Thr Ile Leu Asp Ile Gly Pro Gly | | |
| 145 | 150 | 155 |
| Thr Leu Phe Lys Val Arg Thr Gln Gly Ser Ser Lys Val Lys Cys | | |
| 165 | 170 | 175 |

<210> 285

<211> 126

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (99)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 285

| | |
|---|--|
| Met Ala Ala Phe Ala Thr Ala His Leu Leu Tyr Val Trp Ala Phe Gly | |
| 1 5 10 15 | |
| Phe Ser Pro Leu Gln Pro Gly Leu Leu Leu Leu Ile Ile Leu Ala Pro | |
| 20 25 30 | |
| Gly Pro Tyr Leu Ser Leu Val Leu Gln His Leu Glu Pro Asp Met Val | |
| 35 40 45 | |
| Leu Pro Val Ala Ala Tyr Gly Leu Ile Leu Met Ala Met Leu Trp Arg | |
| 50 55 60 | |
| Gly Leu Ala Gln Gly Gly Ser Ala Gly Trp Gly Ala Leu Leu Phe Thr | |
| 65 70 75 80 | |
| Leu Ser Asp Gly Val Leu Ala Trp Asp Thr Phe Ala Gln Pro Leu Pro | |
| 85 90 95 | |
| His Ala Xaa Leu Val Ile Met Thr Thr Tyr Tyr Ala Ala Gln Leu Leu | |
| 100 105 110 | |
| Ile Thr Leu Ser Ala Leu Arg Ser Pro Val Pro Lys Thr Asp | |
| 115 120 125 | |

<210> 286

<211> 187

<212> PRT

<213> Homo sapiens

<400> 286

| | |
|---|--|
| Met Trp Cys Ala Ser Pro Val Ala Val Val Ala Phe Cys Ala Gly Leu | |
| 1 5 10 15 | |
| Leu Val Ser His Pro Val Leu Thr Gln Gly Gln Glu Ala Gly Gly Arg | |
| 20 25 30 | |
| Pro Gly Ala Asp Cys Glu Val Cys Lys Glu Phe Leu Asn Arg Phe Tyr | |

158

| 35 | | | | | 40 | | | | | 45 | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Lys | Ser | Leu | Ile | Asp | Arg | Gly | Val | Asn | Phe | Ser | Leu | Asp | Thr | Ile | Glu |
| 50 | | | | | | 55 | | | | | 60 | | | | |
| Lys | Glu | Leu | Ile | Ser | Phe | Cys | Leu | Asp | Thr | Lys | Gly | Lys | Glu | Asn | Arg |
| 65 | | | | | 70 | | | | | 75 | | | | | 80 |
| Leu | Cys | Tyr | Tyr | Leu | Gly | Ala | Thr | Lys | Asp | Ala | Ala | Thr | Lys | Ile | Leu |
| | | | | 85 | | | | | 90 | | | | | 95 | |
| Ser | Glu | Val | Thr | Arg | Pro | Met | Ser | Val | His | Met | Pro | Ala | Met | Lys | Ile |
| | | | 100 | | | | | 105 | | | | | 110 | | |
| Cys | Glu | Lys | Leu | Lys | Lys | Leu | Asp | Ser | Gln | Ile | Cys | Glu | Leu | Lys | Tyr |
| | | 115 | | | | | 120 | | | | | 125 | | | |
| Glu | Lys | Thr | Leu | Asp | Leu | Ala | Ser | Val | Asp | Leu | Arg | Lys | Met | Arg | Val |
| | | 130 | | | | 135 | | | | | 140 | | | | |
| Ala | Glu | Leu | Lys | Gln | Ile | Leu | His | Ser | Trp | Gly | Glu | Glu | Cys | Arg | Ala |
| 145 | | | | | 150 | | | | | 155 | | | | | 160 |
| Cys | Ala | Glu | Lys | Thr | Asp | Tyr | Val | Asn | Leu | Ile | Gln | Glu | Leu | Ala | Pro |
| | | | | 165 | | | | | 170 | | | | | 175 | |
| Lys | Tyr | Ala | Ala | Thr | His | Pro | Lys | Thr | Glu | Leu | | | | | |
| | | | | 180 | | | | 185 | | | | | | | |

<210> 287

<211> 214

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (186)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (188)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (189)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (200)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (202)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (203)

<223> Xaa equals any of the naturally occurring L-amino acids

159

<220>

<221> SITE

<222> (204)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (206)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (211)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 287

Met Ser Arg Gly Leu Leu Ala Val Arg Gly Ala Phe Val Gly Ala Ser
 1 5 10 15

Leu Leu Phe Leu Leu Val Asn Val Leu Cys Ala Val Leu Ser His Arg
 20 25 30

Arg Arg Ala Gln Pro Trp Ala Leu Leu Val Arg Val Leu Val Ser
 35 40 45

Asp Ser Leu Phe Val Ile Cys Ala Leu Ser Leu Ala Ala Cys Leu Cys
 50 55 60

Leu Val Ala Arg Arg Ala Pro Ser Thr Ser Ile Tyr Leu Glu Ala Lys
 65 70 75 80

Gly Thr Ser Val Cys Gln Ala Ala Ala Met Gly Gly Ala Met Val Leu
 85 90 95

Leu Tyr Ala Ser Arg Ala Cys Tyr Asn Leu Thr Ala Leu Ala Leu Ala
 100 105 110

Pro Gln Ser Arg Leu Asp Thr Phe Asp Tyr Asp Trp Tyr Asn Val Ser
 115 120 125

Asp Gln Ala Asp Leu Val Asn Asp Leu Gly Asn Lys Gly Tyr Leu Val
 130 135 140

Phe Gly Leu Ile Leu Phe Val Trp Glu Leu Leu Pro Thr Thr Leu Leu
 145 150 155 160

Val Gly Phe Phe Arg Val His Arg Pro Pro Gln Asp Leu Ser Thr Ser
 165 170 175

His Ile Pro Gln Trp Ala Arg Ser Phe Xaa Ser Xaa Xaa Leu Leu Leu
 180 185 190

Leu Thr Gly Ala Trp Ala Leu Xaa Lys Xaa Xaa Xaa Ala Xaa Phe Leu
 195 200 205

Gly Thr Xaa Thr Arg Val
 210

<210> 288

<211> 254

<212> PRT

<213> Homo sapiens

<220>

160

<221> SITE
 <222> (144)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <220>
 <221> SITE
 <222> (212)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <220>
 <221> SITE
 <222> (214)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <220>
 <221> SITE
 <222> (245)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <220>
 <221> SITE
 <222> (248)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <400> 288
 Phe Leu Leu Val Asn Val Leu Cys Ala Val Leu Ser His Arg Arg Arg
 1 5 10 15
 Ala Gln Pro Trp Ala Leu Leu Leu Val Arg Val Leu Val Ser Asp Ser
 20 25 30
 Leu Phe Val Ile Cys Ala Leu Ser Leu Ala Ala Cys Leu Cys Leu Val
 35 40 45
 Ala Arg Arg Ala Pro Ser Thr Ser Ile Tyr Leu Glu Ala Lys Gly Thr
 50 55 60
 Ser Val Cys Gln Ala Ala Ala Met Gly Gly Ala Met Val Leu Leu Tyr
 65 70 75 80
 Ala Ser Arg Ala Cys Tyr Asn Leu Thr Ala Leu Ala Leu Ala Pro Gln
 85 90 95
 Ser Arg Leu Asp Thr Phe Asp Tyr Asp Trp Tyr Asn Val Ser Asp Gln
 100 105 110
 Ala Asp Leu Val Asn Asp Leu Gly Asn Lys Gly Tyr Leu Val Phe Gly
 115 120 125
 Leu Ile Leu Phe Val Trp Glu Leu Leu Pro Thr Thr Leu Leu Val Xaa
 130 135 140
 Phe Phe Arg Val His Arg Pro Pro Gln Asp Leu Ser Thr Ser His Ile
 145 150 155 160
 Leu Asn Gly Gln Val Phe Ala Ser Arg Ser Tyr Phe Phe Asp Arg Ala
 165 170 175
 Gly His Cys Glu Asp Glu Gly Cys Ser Trp Glu His Ser Arg Gly Glu
 180 185 190
 Ser Thr Ser Met Ser Gly Ser Leu Gly Ser Gly Ser Trp Tyr Gly Ala
 195 200 205
 Ile Gly Arg Xaa Pro Xaa Trp Tyr Gly Gly Ser Gln Thr Lys Thr Thr
 210 215 220

161

Pro Leu Ser Leu Gln Cys Arg Gln Arg Thr His Ser Leu Ser Pro Asn
 225 230 235 240

Gly Pro Leu Gln Xaa Pro Ala Xaa Leu Leu Ala Gly Ser Val
 245 250

<210> 289

<211> 221

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (210)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (215)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (217)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 289

Met Gly Gly Met Ile Ile Val Leu Leu Ile Cys Ile Val Trp Phe Pro
 1 5 10 15

Leu Leu Phe Met Ser Leu Ile Lys Ser Val Ala Gly Val Ile Asn Gln
 20 25 30

Pro Leu Asp Val Ser Val Thr Ile Thr Leu Gly Gly Tyr Gln Pro Ile
 35 40 45

Phe Thr Met Ser Ala Gln Gln Ser Gln Leu Lys Ile Met Asp Gln Gln
 50 55 60

Ser Phe Asn Lys Phe Ile Gln Ala Phe Ser Arg Asp Thr Gly Ala Met
 65 70 75 80

Gln Phe Leu Glu Asn Tyr Glu Lys Glu Asp Ile Thr Val Ala Glu Leu
 85 90 95

Glu Gly Asn Ser Asn Ser Leu Trp Thr Ile Ser Pro Pro Ser Lys Gln
 100 105 110

Lys Met Ile His Glu Leu Leu Asp Pro Asn Ser Ser Phe Ser Val Val
 115 120 125

Phe Ser Trp Ser Ile Gln Arg Asn Leu Ser Leu Gly Ala Lys Ser Glu
 130 135 140

Ile Ala Thr Asp Lys Leu Ser Phe Pro Leu Lys Asn Ile Thr Arg Lys
 145 150 155 160

Asn Ile Ala Lys Met Ile Ala Gly Asn Ser Thr Glu Ser Ser Lys Thr
 165 170 175

Pro Val Thr Ile Glu Lys Ile Tyr Pro Tyr Tyr Val Lys Ala Pro Ser
 180 185 190

162

Asp Ser Asn Ser Lys Pro Ile Lys Gln Leu Leu Ser Glu Asn Asn Ser
 195 200 205

Trp Xaa Leu Pro Ser Phe Xaa Gln Xaa His Thr Leu Asn
 210 215 220

<210> 290
 <211> 135
 <212> PRT
 <213> Homo sapiens

<400> 290
 Met Ala Phe Lys Leu Leu Ile Leu Leu Ile Gly Thr Trp Ala Leu Phe
 1 5 10 15

Phe Arg Lys Arg Arg Ala Asp Met Pro Arg Val Phe Val Phe Arg Ala
 20 25 30

Leu Leu Leu Val Leu Ile Phe Leu Phe Val Val Ser Tyr Trp Leu Phe
 35 40 45

Tyr Gly Val Arg Ile Leu Asp Ser Arg Asp Arg Asn Tyr Gln Gly Ile
 50 55 60

Val Gln Tyr Ala Val Ser Leu Val Asp Ala Leu Leu Phe Ile His Tyr
 65 70 75 80

Leu Ala Ile Val Leu Leu Glu Leu Arg Gln Leu Gln Pro Met Phe Thr
 85 90 95

Leu Gln Val Val Pro Leu His Arg Trp Arg Val Pro Leu Leu Gln Pro
 100 105 110

Gly Thr Pro Glu Tyr Pro Ala Ser Ser Ile Gly Gly Pro Arg Lys Leu
 115 120 125

Leu Gln Arg Phe His His Leu
 130 135

<210> 291
 <211> 295
 <212> PRT
 <213> Homo sapiens

<400> 291
 Met Leu Cys Cys Trp Phe Pro Trp Arg Ile Leu Ala Ala Gly Gln Val
 1 5 10 15

Pro Tyr Ser Pro His Ser Pro Gln Val Ala Gly Cys Asp Leu Thr Arg
 20 25 30

Cys Glu Ser Gly Gly Ala Arg Ala Leu Ser Ile Gln Arg Ala Ala Leu
 35 40 45

Val Val Leu Glu Asn Tyr Tyr Lys Asp Phe Thr Ile Tyr Asn Pro Asn
 50 55 60

Leu Leu Thr Ala Ser Lys Phe Arg Ala Ala Lys His Met Ala Gly Leu
 65 70 75 80

Lys Val Tyr Asn Val Asp Gly Pro Ser Asn Asn Ala Thr Gly Gln Ser
 85 90 95

163

Arg Ala Met Ile Ala Ala Ala Ala Arg Arg Arg Asp Ser Ser His Asn
 100 105 110
 Glu Leu Tyr Tyr Glu Glu Ala Glu His Glu Arg Arg Val Lys Lys Arg
 115 120 125
 Lys Ala Arg Leu Val Val Ala Val Glu Glu Ala Phe Ile His Ile Gln
 130 135 140
 Arg Leu Gln Ala Glu Glu Gln Gln Lys Ala Pro Gly Glu Val Met Asp
 145 150 155 160
 Pro Arg Glu Ala Ala Gln Ala Ile Phe Pro Ser Met Ala Arg Ala Leu
 165 170 175
 Gln Lys Tyr Leu Arg Ile Thr Arg Gln Gln Asn Tyr His Ser Met Glu
 180 185 190
 Ser Ile Leu Gln His Leu Ala Phe Cys Ile Thr Asn Gly Met Thr Pro
 195 200 205
 Lys Ala Phe Leu Glu Arg Tyr Leu Ser Ala Gly Pro Thr Leu Gln Tyr
 210 215 220
 Asp Lys Asp Arg Trp Leu Ser Thr Gln Trp Arg Leu Val Ser Asp Glu
 225 230 235 240
 Ala Val Thr Asn Gly Leu Arg Asp Gly Ile Val Phe Val Leu Lys Cys
 245 250 255
 Leu Asp Phe Ser Leu Val Val Asn Val Lys Lys Ile Pro Phe Ile Ile
 260 265 270
 Leu Ser Glu Glu Phe Ile Asp Pro Lys Ser His Lys Phe Val Leu Arg
 275 280 285
 Leu Gln Ser Glu Thr Ser Val
 290 295

<210> 292
 <211> 85
 <212> PRT
 <213> Homo sapiens

<400> 292
 Met Asp Thr Tyr Phe Ile Leu Trp Ala Ile Pro Val Thr Ile Ile Ile
 1 5 10 15
 Cys Phe Ser Trp Leu Glu Tyr Ser Gln Thr Trp Ala Leu Gly Ala Ser
 20 25 30
 Cys Ser Leu Pro Gln Cys Pro Phe Asp Val Met Leu Ser Leu Phe Leu
 35 40 45
 Val His Pro Tyr Phe Pro Thr Val Trp Asp His Leu Cys Phe Pro His
 50 55 60
 Pro Ser Pro Glu Ser Ser Pro Phe Ser Lys Cys Ser Leu Val Ala Trp
 65 70 75 80
 Leu Glu Asn Gly Ala
 85

<210> 293
 <211> 196
 <212> PRT
 <213> Homo sapiens

<400> 293
 Thr Gln Arg Met Ser Gly Lys His Tyr Lys Gly Pro Glu Val Ser Cys
 1 5 10 15
 Cys Ile Lys Tyr Phe Ile Phe Gly Phe Asn Val Ile Phe Trp Phe Leu
 20 25 30
 Gly Ile Thr Phe Leu Gly Ile Gly Leu Trp Ala Trp Asn Glu Lys Gly
 35 40 45
 Val Leu Ser Asn Ile Ser Ser Ile Thr Asp Leu Gly Gly Phe Asp Pro
 50 55 60
 Val Trp Leu Phe Leu Val Val Gly Gly Val Met Phe Ile Leu Gly Phe
 65 70 75 80
 Ala Gly Cys Ile Gly Ala Leu Arg Glu Asn Thr Phe Leu Leu Lys Phe
 85 90 95
 Phe Ser Val Phe Leu Gly Ile Ile Phe Phe Leu Glu Leu Thr Ala Gly
 100 105 110
 Val Leu Ala Phe Val Phe Lys Asp Trp Ile Lys Asp Gln Leu Tyr Phe
 115 120 125
 Phe Ile Asn Asn Asn Ile Arg Ala Tyr Arg Asp Asp Ile Asp Leu Gln
 130 135 140
 Asn Leu Ile Asp Phe Thr Gln Glu Tyr Ile Pro Met Gln Val Glu Ser
 145 150 155 160
 Asp Val Ala Phe His Ser Pro Ala Ala Leu Lys Ile Pro Gln Lys Met
 165 170 175
 Ser Ser Thr Leu Ser Val Ala Met Met Pro Gly Lys Asn Gln Lys Leu
 180 185 190
 Thr Ser Arg Leu
 195

<210> 294
 <211> 58
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (8)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <220>
 <221> SITE
 <222> (16)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <400> 294

165

Val Ser Leu Lys Leu Val Ile Xaa Leu Ser Trp Asn Leu Ile Thr Xaa
 1 5 10 15
 Val Trp Phe His Lys Asn Leu Thr Phe Gly Ser Trp Leu Ile His Trp
 20 25 30
 Glu Gly Pro Ser Gly Phe Phe Asn Phe Gly Gly Ser Gly Leu Gly Lys
 35 40 45
 Phe Phe His Leu Lys Leu Asn Leu Met Gly
 50 55

<210> 295
 <211> 133
 <212> PRT
 <213> Homo sapiens

<400> 295
 Met His Gly Ala Arg Leu Phe Val Cys Leu Phe Val Cys Phe Arg Gln
 1 5 10 15
 Ser Cys Tyr Val Ala Gln Ala Gly Val Gln Trp His Asn His Ser Ser
 20 25 30
 Leu Gln Pro Leu Ser Pro Gly Phe Lys Arg Phe Phe Cys Leu Asn Leu
 35 40 45
 Pro Ser Ser Trp Asp Tyr Arg His Met Ala Thr Cys Pro Trp Leu Ile
 50 55 60
 Phe Val Phe Leu Val Glu Met Glu Phe Arg His Val Gly Gln Ala Gly
 65 70 75 80
 Leu Gly Leu Leu Thr Ser Ser Asp Leu Pro Ala Leu Ala Phe Gln Ser
 85 90 95
 Ala Gly Ile Thr Gly Leu Ser His His Ala Trp Pro Gly Arg Phe Leu
 100 105 110
 Lys Lys Val Ile Glu Ile Cys Ser Cys Pro Val Pro Arg Gly Ser His
 115 120 125
 Ala Gly Leu Phe Ser
 130

<210> 296
 <211> 74
 <212> PRT
 <213> Homo sapiens

<400> 296
 Ser Lys Thr Gly Ile Val Leu Gln Thr Phe Arg Ala Glu Phe Gln Glu
 1 5 10 15
 Leu Lys Ser Glu Lys Gln Gln Ala Ala Phe Pro Lys Arg Tyr Thr Cys
 20 25 30
 Phe Gly His Gln Arg Arg Thr Glu Leu Arg Ala Ala Val Glu Asn Leu
 35 40 45
 Lys His Ser Ala Glu Phe Leu Ser Ala Pro Leu Ala Asn Lys Leu Lys
 50 55 60

166

Cys Gln Thr Ala Leu Ala Ala Gly Tyr Phe
65 70

<210> 297
<211> 133
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (34)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (60)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (69)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (96)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 297
Met Ala Pro Ala Gly Cys Cys Cys Cys Cys Cys Phe Trp Gly Gly Ala
1 5 10 15
Val Ala Ala Ala Gly Ala Ala Arg Arg Val Leu Leu Leu Leu Leu Leu
20 25 30
Gly Xaa Leu Ser Ala Arg Leu Arg Pro Gly Ala Leu Ala Thr Glu His
35 40 45
Tyr Ser Pro Leu Ala Leu Leu Lys Gln Glu Leu Xaa His Arg Gln Gln
50 55 60
Gln Glu Ala Pro Xaa Gly Gly Gly Gly Cys Ser Pro Gln Ser Gly Asp
65 70 75 80
Trp Gly Asp Gln Tyr Ser Ala Glu Cys Gly Glu Ser Ser Phe Leu Xaa
85 90 95
Phe His Asp Ser Asp Cys Glu Pro Gln Gly Ser Ser Pro Cys Asp Ser
100 105 110
Leu Leu Ser Leu Asn Thr Ala Lys Ile Leu Ser Gln Ala Lys Ser Ile
115 120 125
Ala Glu Gln Lys Arg
130

<210> 298
<211> 108
<212> PRT
<213> Homo sapiens

<220>

<221> SITE

<222> (89)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (91)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (102)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (106)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 298

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Thr | Ser | Gln | Asn | Leu | Trp | Val | Ile | Val | Val | Ile | Ala | Asn | Ser | Ile |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Val | Ile | Val | Ala | Gln | Tyr | Arg | Asp | Glu | Gly | Asn | Arg | Phe | Cys | Asn |
| | | | 20 | | | | | 25 | | | | | 30 | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gln | Met | Ile | Leu | Gly | Ser | Glu | Ser | Thr | Leu | Pro | Leu | Thr | Ser | Tyr | Met |
| | | 35 | | | | | 40 | | | | | 45 | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Thr | Ser | Ser | Asn | Phe | His | His | Leu | Ser | Met | Leu | Gln | Phe | Pro | His | Arg |
| | 50 | | | | | 55 | | | | | 60 | | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gln | Asp | Gly | Cys | Gly | Gly | Arg | Gly | Thr | Thr | Val | Gln | Ile | His | His | Pro |
| 65 | | | | 70 | | | | | | 75 | | | | | 80 |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Lys | Phe | Lys | Met | Leu | Gln | Asn | Leu | Xaa | Arg | Xaa | Trp | Trp | Leu | Ile | Pro |
| | | | | 85 | | | | | 90 | | | | | 95 | |

| | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Ile | Pro | Ala | Leu | Xaa | Glu | Val | Lys | Xaa | Asp | Gly |
| | | | 100 | | | | | 105 | | | |

<210> 299

<211> 68

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (19)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 299

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asn | Phe | Leu | Glu | Pro | Lys | Cys | Asp | Ala | Thr | Ser | Gly | Lys | Phe | His | Asn |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Ser | Xaa | Val | Ile | Asp | Cys | Ser | Gly | Asn | Ala | Gly | Thr | His | His | Glu |
| | | | 20 | | | | | 25 | | | | | 30 | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Tyr | Ser | Ala | Ser | Ser | Lys | Glu | Ile | Pro | Val | Ser | Ser | Tyr | Ile | Ser |
| | | 35 | | | | | 40 | | | | | 45 | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Phe | Ser | His | Met | Pro | Asp | Arg | Tyr | Leu | Ser | Ser | Phe | Thr | Val | Arg | Tyr |
| | 50 | | | | | 55 | | | | | | 60 | | | |

168

Phe Cys Val Glu
65

<210> 300
<211> 194
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (168)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 300
Met Met Trp Leu Leu Leu Thr Thr Thr Cys Leu Ile Cys Gly Thr Leu
1 5 10 15
Asn Ala Gly Gly Phe Leu Asp Leu Glu Asn Glu Val Asn Pro Glu Val
20 25 30
Trp Met Asn Thr Ser Glu Ile Ile Ile Tyr Asn Gly Tyr Pro Ser Glu
35 40 45
Glu Tyr Glu Val Thr Thr Glu Asp Gly Tyr Ile Leu Leu Val Asn Arg
50 55 60
Ile Pro Tyr Gly Arg Thr His Ala Arg Ser Thr Gly Pro Arg Pro Val
65 70 75 80
Val Tyr Met Gln His Ala Leu Phe Ala Asp Asn Ala Tyr Trp Leu Glu
85 90 95
Asn Tyr Ala Asn Gly Ser Leu Gly Phe Leu Leu Ala Asp Ala Gly Tyr
100 105 110
Asp Val Trp Met Gly Asn Ser Arg Gly Asn Thr Trp Ser Arg Arg His
115 120 125
Lys Thr Leu Ser Glu Thr Asp Glu Lys Phe Trp Ala Phe Ser Phe Asp
130 135 140
Glu Met Ala Lys Tyr Asp Leu Pro Gly Val Ile Asp Phe Ile Val Asn
145 150 155 160
Lys Thr Gly Gln Glu Lys Leu Xaa Phe Ile Gly His Ser Leu Gly Thr
165 170 175
Thr Ile Gly Phe Val Ala Phe Ser Pro Cys Leu Asn Trp His Lys Glu
180 185 190

Ser Lys

<210> 301
<211> 87
<212> PRT
<213> Homo sapiens

<400> 301
Met Arg Phe Ile Trp Leu Met Phe Leu Gln Ala Val Gln Ala Ser Gly
1 5 10 15

169

Lys Gly Leu Arg Lys Leu Pro His Thr Val Glu Asp Glu Gly Glu Pro
 20 25 30
 Glu Cys Ala Asp Tyr Met Val Arg Glu Trp Lys Gln Glu Arg Gly Ala
 35 40 45
 Gly Gly Ala Arg Ile Phe Ser Thr Ile Ser Ser Trp Met Ser Thr Val
 50 55 60
 Ala His Ala Cys Asn Pro Ser Thr Leu Gly Ala Gln Asp Gly Arg Ile
 65 70 75 80
 Thr Ser Ala Gln Glu Phe Asn
 85

<210> 302
 <211> 90
 <212> PRT
 <213> Homo sapiens

<400> 302
 Met Asp Arg Arg Arg Met Ala Leu Arg Pro Gly Ser Arg Arg Pro Thr
 1 5 10 15
 Ala Phe Phe Phe His Ser Arg Trp Leu Val Pro Asn Leu Leu Ala Phe
 20 25 30
 Phe Leu Gly Leu Ser Gly Ala Gly Pro Ile His Leu Pro Met Pro Trp
 35 40 45
 Pro Asn Gly Arg Arg His Arg Val Leu Asp Pro His Thr Gln Leu Ser
 50 55 60
 Thr His Glu Ala Pro Gly Arg Trp Lys Pro Val Ala Pro Arg Arg Met
 65 70 75 80
 Lys Ala Cys Pro Gln Val Leu Leu Glu Trp
 85 90

<210> 303
 <211> 34
 <212> PRT
 <213> Homo sapiens

<400> 303
 Met Met Ser Ile His Cys Val Gln Pro Leu Leu Pro Leu Phe Leu Pro
 1 5 10 15
 Ser Ser Tyr Phe Lys Gln Phe Leu Leu Leu Pro Trp Thr Phe Gly Val
 20 25 30
 Ala Leu

<210> 304
 <211> 47
 <212> PRT
 <213> Homo sapiens

170

<220>

<221> SITE

<222> (31)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (32)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 304

His Thr Phe Ser Asn Cys Leu Leu Glu Arg Leu Tyr Gln Ala Arg Cys
 1 5 10 15

Ser Cys Leu Met Pro Val Ile Leu Ala Leu Trp Glu Ala Glu Xaa Xaa
 20 25 30

Gly Gln Leu Glu Leu Arg Ser Ser Arg Pro Ala Trp Ala Thr Trp
 35 40 45

<210> 305

<211> 245

<212> PRT

<213> Homo sapiens

<400> 305

Met Phe Leu Leu Phe Leu Leu Thr Cys Glu Leu Ala Ala Glu Val Ala
 1 5 10 15

Ala Glu Val Glu Lys Ser Ser Asp Gly Pro Gly Ala Ala Gln Glu Pro
 20 25 30

Thr Trp Leu Thr Asp Val Pro Ala Ala Met Glu Phe Ile Ala Ala Thr
 35 40 45

Glu Val Ala Val Ile Gly Phe Phe Gln Asp Leu Glu Ile Pro Ala Val
 50 55 60

Pro Ile Leu His Ser Met Val Gln Lys Phe Pro Gly Val Ser Phe Gly
 65 70 75 80

Ile Ser Thr Asp Ser Glu Val Leu Thr His Tyr Asn Ile Thr Gly Asn
 85 90 95

Thr Ile Cys Leu Phe Arg Leu Val Asp Asn Glu Gln Leu Asn Leu Glu
 100 105 110

Asp Glu Asp Ile Glu Ser Ile Asp Ala Thr Lys Leu Ser Arg Phe Ile
 115 120 125

Glu Ile Asn Ser Leu His Met Val Thr Glu Tyr Asn Pro Val Ala Ser
 130 135 140

Pro Glu Tyr Glu Glu Asn Met His Arg Tyr Gln Lys Ala Ala Lys Leu
 145 150 155 160

Phe Gln Gly Lys Ile Leu Phe Ile Leu Val Asp Ser Gly Met Lys Glu
 165 170 175

Asn Gly Lys Val Ile Ser Phe Phe Lys Leu Lys Glu Ser Gln Leu Pro
 180 185 190

Ala Leu Ala Ile Tyr Gln Thr Leu Asp Asp Glu Trp Asp Thr Leu Pro
 195 200 205

171

Thr Ala Glu Val Ser Val Glu His Val Gln Asn Phe Cys Asp Gly Phe
 210 215 220
 Leu Ser Gly Lys Leu Leu Lys Glu Asn Arg Glu Ser Glu Gly Lys Thr
 225 230 235 240
 Pro Lys Val Glu Leu
 245

<210> 306
 <211> 140
 <212> PRT
 <213> Homo sapiens

<400> 306
 Met Phe Pro Leu His Leu Ala Val Leu Phe Gly Phe Ser Asp Cys Cys
 1 5 10 15
 Arg Lys Leu Leu Ser Ser Gly Gln Leu Tyr Ser Ile Val Ser Ser Leu
 20 25 30
 Ser Asn Glu His Val Leu Ser Ala Gly Phe Asp Ile Asn Thr Pro Asp
 35 40 45
 Asn Leu Gly Arg Thr Cys Leu His Ala Ala Ala Ser Gly Gly Asn Val
 50 55 60
 Glu Cys Leu Asn Leu Leu Leu Ser Ser Gly Ala Asp Leu Arg Arg Arg
 65 70 75 80
 Asp Lys Phe Gly Arg Thr Pro Leu His Tyr Ala Ala Ala Asn Gly Ser
 85 90 95
 Tyr Gln Cys Ala Val Thr Leu Val Thr Ala Gly Ala Gly Val Asn Glu
 100 105 110
 Ala Asp Cys Lys Gly Cys Ser Pro Leu His Tyr Ala Ala Ala Ser Asp
 115 120 125
 Thr Tyr Arg Arg Ala Glu Pro His Thr Pro Ser Ser
 130 135 140

<210> 307
 <211> 110
 <212> PRT
 <213> Homo sapiens

<400> 307
 Met Lys Arg Tyr Ile Ile Ser Leu Gln Ser Pro Leu Ser His Ser Ser
 1 5 10 15
 Met Trp Pro Ala Tyr Leu Leu Pro Ile Met Leu Leu Ile His Leu Gln
 20 25 30
 Ala Ile Cys His Gln Ile Lys Lys Gln Gln Thr Glu Gly Gln Ser Gln
 35 40 45
 Asp Val Leu Thr His His Cys Asn Phe Leu Leu Glu Met Ile Pro Phe
 50 55 60
 Arg Lys Arg Leu Val Glu Ile Gly Val Lys Gly Thr Leu Gln Ile Ser

:172

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| 65 | | | | | 70 | | | | | 75 | | | | 80 | |
| Pro | Val | Leu | Ser | Tyr | Phe | Gln | Leu | Tyr | Arg | Gln | Glu | Gln | Phe | Lys | Ser |
| | | | | 85 | | | | | 90 | | | | | 95 | |
| Lys | Glu | Phe | Ser | Arg | Phe | Leu | Gln | Cys | His | Lys | Ala | Val | Ser | | |
| | | | 100 | | | | | 105 | | | | | 110 | | |

<210> 308
 <211> 107
 <212> PRT
 <213> Homo sapiens

<400> 308
 Met Pro Pro Pro Phe Leu Arg Lys Pro Leu Ile Leu Cys Val Phe Leu
 1 5 10 15
 Pro Thr Glu Gly Asn Cys Gly Gly Ser Ser Leu Ala Phe Leu Leu Asn
 20 25 30
 Phe Ala Gly Asn Ser Pro Gln Phe Leu Ser Glu Val Arg Thr Val His
 35 40 45
 Tyr Gln Arg Asp Trp Thr Leu Tyr Pro Leu Ala Lys Trp Glu Lys Ile
 50 55 60
 Leu Pro Ala His Ser Thr Pro Pro Trp Pro Ser Pro Thr Pro His Pro
 65 70 75 80
 Gln Gln His Phe His Gly Asn Pro Asp Gly Arg Val Val Leu Trp Leu
 85 90 95
 Ser Cys Asp Arg Leu Ala Phe Ile Leu Glu Ser
 100 105

<210> 309
 <211> 251
 <212> PRT
 <213> Homo sapiens

<400> 309
 Met Gly Pro Pro Gly Ala Gly Val Ser Cys Arg Gly Gly Cys Gly
 1 5 10 15
 Phe Ser Arg Leu Leu Ala Trp Cys Phe Leu Leu Ala Leu Ser Pro Gln
 20 25 30
 Ala Pro Gly Ser Arg Gly Ala Glu Ala Val Trp Thr Ala Tyr Leu Asn
 35 40 45
 Val Ser Trp Arg Val Pro His Thr Gly Val Asn Arg Thr Val Trp Glu
 50 55 60
 Leu Ser Glu Glu Gly Val Tyr Gly Gln Asp Ser Pro Leu Glu Pro Val
 65 70 75 80
 Ala Gly Val Leu Val Pro Pro Asp Gly Pro Gly Ala Leu Asn Ala Cys
 85 90 95
 Asn Pro His Thr Asn Phe Thr Val Pro Thr Val Trp Gly Ser Thr Val
 100 105 110

173

Gln Val Ser Trp Leu Ala Leu Ile Gln Arg Gly Gly Gly Cys Thr Phe
 115 120 125
 Ala Asp Lys Ile His Leu Ala Tyr Glu Arg Gly Ala Ser Gly Ala Val
 130 135 140
 Ile Phe Asn Phe Pro Gly Thr Arg Asn Glu Val Ile Pro Met Ser His
 145 150 155 160
 Pro Gly Ala Val Asp Ile Val Ala Ile Met Ile Gly Asn Leu Lys Gly
 165 170 175
 Thr Lys Ile Leu Gln Ser Ile Gln Arg Gly Ile Gln Val Thr Met Val
 180 185 190
 Ile Glu Val Gly Lys Lys His Gly Pro Trp Val Asn His Tyr Ser Ile
 195 200 205
 Phe Phe Arg Phe Cys Val Leu Phe Tyr Tyr Tyr Gly Gly Asn Cys Gly
 210 215 220
 Leu Phe Tyr Leu Leu Phe Cys Ser Lys Ala Thr Glu Cys Lys Ser Ser
 225 230 235 240
 Lys Gln Glu Ala Glu Ala Ile Lys Gly Arg Cys
 245 250

<210> 310
 <211> 124
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (78)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (108)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (111)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 310
 Met Leu Thr Gln Ser Gln Gln Val Leu Arg Gly Ile Leu Leu Phe Leu
 1 5 10 15
 Gln Asn Ile Leu Gln Val Ser Trp Gly Ser Pro Leu Ala Leu Ala Ser
 20 25 30
 Pro Pro Ser Pro Ser Leu Gln Pro Gly Asn Gly Leu Ala Ser Ser Leu
 35 40 45
 Leu Ala Leu Gln Pro Gly Leu Ala Gly Pro Trp Ala Gly Pro Gln Glu
 50 55 60
 Pro Ser Pro Ala Met Cys Phe Pro Lys Lys Arg Ser Leu Xaa Pro Asn
 65 70 75 80
 Leu Arg Lys Gln Trp Ala Ser Ile His Ile Asn Asp Pro Arg Gly Thr

174

| | | | | | |
|---|-----|--|-----|--|-----|
| | 85 | | 90 | | 95 |
| Leu Cys Pro Arg Cys Thr Gly Cys Asn Gln Arg Xaa Ser Gly Xaa Ser | | | | | |
| | 100 | | 105 | | 110 |
| Gly Leu Ile Trp Arg Asp Arg Phe Tyr His His Pro | | | | | |
| | 115 | | 120 | | |

<210> 311
 <211> 87
 <212> PRT
 <213> Homo sapiens

<400> 311
 Met Thr Trp Ser Phe Cys Phe Ala Leu Phe Cys Phe Val Leu Phe Phe
 1 5 10 15
 Ala Ala Ser Leu Ile Gly Tyr Ile Leu Leu Pro Ser Ala Ser Pro Arg
 20 25 30
 Asn His Arg Arg Pro Asn Asn Glu Ala Arg Val Gly Thr Pro Gly Gln
 35 40 45
 Leu Asp Asp Glu Leu Lys Gly Arg Gln Pro Leu Ala Ser Arg Leu Glu
 50 55 60
 Thr Ser Gln Cys Thr Gln Gly Leu Leu Ala Ser Arg Pro Ser Gly Val
 65 70 75 80
 Ser Lys Ala Leu Leu Tyr Pro
 85

<210> 312
 <211> 84
 <212> PRT
 <213> Homo sapiens

<400> 312
 Met Glu Trp Gln Phe Gly Lys Pro Ser Phe Leu Leu Ser Leu Leu Met
 1 5 10 15
 Leu Leu Val Leu Glu Trp Lys Ala Leu Cys Gly Val Arg Leu Gly His
 20 25 30
 Leu Gly Leu Gln Val Pro Asn Pro Ser Leu Lys Ser Thr Cys Leu Trp
 35 40 45
 Pro Leu Arg Ser Leu Cys Pro Trp Arg Leu Tyr Pro Ile Lys Ile Met
 50 55 60
 Ile Ser Leu Pro Leu Pro Ser Leu Gln Leu Pro Ser Ser Pro His Arg
 65 70 75 80
 Pro Phe Gln Leu

<210> 313
 <211> 71
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (4)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (10)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 313
 Leu Pro Gly Xaa Cys Phe Asn His Leu Xaa Ile Asn Phe Trp Lys Lys
 1 5 10 15
 Ile Ile Ile Phe Thr Leu Lys Phe Pro Tyr Ser Lys Tyr Ser Ile Ser
 20 25 30
 Val Trp Gln Met Asp Glu Trp Ala Asp Ile Ile Gly Ser Tyr His Val
 35 40 45
 Asp Tyr Glu Glu Val Gln Ser Ile Gln Asn Lys Asn Thr Lys His Ser
 50 55 60
 Asn Lys Pro Arg Val Cys Gln
 65 70

<210> 314
 <211> 142
 <212> PRT
 <213> Homo sapiens

<400> 314
 Met Leu Trp Thr Thr Leu Thr Gly Val Ser Leu Ala Leu Phe Pro Val
 1 5 10 15
 Ala Gln Ala Pro Thr Ala Leu Val Ala Leu Ala Val Ala Tyr Gly Phe
 20 25 30
 Thr Ser Gly Ala Leu Ala Pro Leu Ala Phe Ser Val Leu Pro Glu Leu
 35 40 45
 Ile Gly Thr Arg Arg Ile Tyr Cys Gly Leu Gly Leu Leu Gln Met Ile
 50 55 60
 Glu Ser Ile Gly Gly Leu Leu Gly Pro Pro Leu Ser Gly Tyr Leu Arg
 65 70 75 80
 Asp Val Thr Gly Asn Tyr Thr Ala Ser Phe Val Val Ala Gly Ala Phe
 85 90 95
 Leu Leu Ser Gly Ser Gly Ile Leu Leu Thr Leu Pro His Phe Phe Cys
 100 105 110
 Phe Ser Thr Thr Thr Ser Gly Pro Gln Asp Leu Val Thr Glu Ala Leu
 115 120 125
 Asp Thr Lys Val Pro Leu Pro Lys Glu Gly Leu Glu Glu Asp
 130 135 140

<210> 315
 <211> 84

176

<212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (19)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 315
 Met Phe Leu Ser Gly Lys Pro Gly Glu Ser Tyr Leu Ser His Leu Pro
 1 5 10 15
 Cys Leu Xaa Phe Phe Phe Phe Phe Gly Trp Ser Cys Cys Leu Asp
 20 25 30
 Asp Ala Phe Thr Met Gln Glu Arg Val Phe Val Lys Asp Ile Phe Glu
 35 40 45
 Asp Trp Leu Phe His Ile Val Leu His Ser Leu Thr Val Ala Lys Cys
 50 55 60
 Thr Val Asp Phe His Asp His Cys Ile Phe Leu Val Ile Glu Met Tyr
 65 70 75 80
 Leu Leu Cys Phe

<210> 316
 <211> 88
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (62)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 316
 Met Phe Pro Ile Leu Ser Ile Thr Thr Leu Ser Ile Leu Ala Phe Phe
 1 5 10 15
 Leu Trp Leu Ser Val Thr Ser His Phe Tyr Arg Gln Lys Thr Gly Phe
 20 25 30
 His His Ser Pro Ser Phe Tyr Leu Ile Val Gln Ile Trp Asp Thr Tyr
 35 40 45
 Ala Asp Ile Val Ala Ser Glu Tyr Val Phe Pro Trp Arg Xaa Thr Leu
 50 55 60
 Ser Ser Arg Glu Gln Cys Leu Ser Val Val Pro Val Ala Phe Ser Leu
 65 70 75 80
 Ile Asp Phe Ile Ser Lys Val Ser
 85

<210> 317
 <211> 127
 <212> PRT
 <213> Homo sapiens

<400> 317

177

Met Met Pro Thr Tyr Ala Ile Cys Met Val Leu Val Phe Leu Leu Leu
 1 5 10 15
 Val His Leu His Ile Ile Asn Thr Asn Thr His Thr His Thr His Thr
 20 25 30
 His Thr His Thr Gly Leu Leu Pro Glu Pro Tyr Met Leu Tyr Phe Gln
 35 40 45
 Phe Leu Ser Val Leu Arg Gly Tyr Ile Leu Ser Arg Trp Thr Asp Arg
 50 55 60
 Glu Tyr Thr Trp Ile Ser Thr Lys Ile Tyr Ser Pro Asn Ser Pro Glu
 65 70 75 80
 Pro Pro Ala Ser Cys Pro Ser Pro Thr Gln Ser Ile Ser Arg His Ala
 85 90 95
 Val Gln Gly Ser Thr Phe Leu Lys Ala Gln Leu Pro Thr Ser Glu Gln
 100 105 110
 Val Gln Ile His Pro Leu His Pro Pro Ile His Leu Ser Pro Leu
 115 120 125

<210> 318

<211> 83

<212> PRT

<213> Homo sapiens

<400> 318

Met Thr Ser Leu Ala Arg Leu Pro Cys Ser Tyr Leu Cys Leu Pro Cys
 1 5 10 15
 Gln Leu Ser Ser Cys Cys Ala Phe Ser Gln Pro Ile Ser Ala Leu Leu
 20 25 30
 Pro Ser Pro Ser Thr Pro Val Leu Leu Ser Ala Pro Arg Pro Ser Ser
 35 40 45
 Gln Gly Val Pro Gly Thr Arg Ser Glu Phe Pro Ser Thr Pro Phe Cys
 50 55 60
 Leu Pro Ser Phe Pro Arg Glu Ser Phe Leu Asp Ser Phe His Leu Val
 65 70 75 80
 Ser Ser His

<210> 319

<211> 86

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (64)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (66)

<223> Xaa equals any of the naturally occurring L-amino acids

178

<220>

<221> SITE

<222> (75)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 319

Met Ala Lys Ala Pro Phe Tyr His Leu Leu Phe Cys Phe Gly Ile Trp
1 5 10 15Ser Asp Ser Tyr Ser Ser Leu Gly Leu Ala Gln Trp Arg Asn Trp Cys
20 25 30Ser Tyr Cys Thr Gly Leu Cys Thr Pro Cys Asn Cys Asp Val Tyr Asp
35 40 45Cys Ser Ser Cys Phe Pro Ile Leu His Phe Gln Ser Pro Arg Ala Xaa
50 55 60Leu Xaa Arg Ile Thr Ser Thr Val Asn His Xaa Arg Asp Cys Thr Thr
65 70 75 80Arg His Val Gly Gly Lys
85

<210> 320

<211> 70

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (2)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (13)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (21)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (22)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 320

Ile Xaa Gly Glu Pro Arg Phe Leu Gly Thr Met Pro Xaa Leu Glu Phe
1 5 10 15Gly Ser Pro Pro Xaa Xaa Phe Gln Ala Gly Pro Glu Leu Pro Glu Asn
20 25 30Asn Ser Gly Gln Leu Thr Thr Ser Asp Ser Ser Pro Pro Asn Met Ala
35 40 45Tyr Pro Cys Ser Ser Asp Val Ile Leu Val Ala Ser Val Asn Ser Val
50 55 60

Cys His Ala Val Gln Thr

65

70

<210> 321
 <211> 81
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (40)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (42)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (53)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 321
 Met Arg Trp Arg Lys Pro Leu Cys Leu Trp Cys Leu Leu Thr Gln Gly
 1 5 10 15

Glu Thr Glu Ala Gln Ala Gly Gln Pro Leu Ala Trp Gly Gly Gly Trp
 20 25 30

Val Val Leu Arg Pro Val Thr Xaa Pro Xaa Gln His Pro Pro Val Asp
 35 40 45

Pro Leu Pro Ala Xaa Ala Arg Pro Glu Ser Cys Ser Gln Ala Gln Thr
 50 55 60

Leu Ala Cys Pro Ser Gly Asp Ala Gly Gln Tyr Ser Ser Leu Gln Pro
 65 70 75 80

Ser

<210> 322
 <211> 2
 <212> PRT
 <213> Homo sapiens

<400> 322
 Arg Ala
 1

<210> 323
 <211> 138
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (137)
 <223> Xaa equals any of the naturally occurring L-amino acids

180

<400> 323

Met Thr Ser Gly Pro Arg Gly Val Val His Phe Tyr Gly Tyr Ser Val
 1 5 10 15

Val Ser Thr Leu Ala Leu Leu Val Ser Ile Ala Phe Pro Ile Pro Ile
 20 25 30

Cys Gln Gln Trp Glu Pro Ser Tyr Lys Arg Val Lys Ala Leu Ser Ile
 35 40 45

Val Gly Gly Asp Pro His Leu Ile Leu Leu Ala Ser Thr Thr Val Leu
 50 55 60

Val Gly Ala Ile Val Ser Thr Val Gln Asn Phe Leu Phe Trp His Met
 65 70 75 80

Lys Asp His Gly Ser Gly Glu Leu Val Met Gly Phe Ser Val Ala Leu
 85 90 95

Ser Leu Leu Gly Glu Ile Leu Leu His Pro Phe Lys Ala Thr Leu Leu
 100 105 110

Arg Lys Leu Ser Arg Thr Gly Leu Val Gly Leu Gly Leu Ser Cys Leu
 115 120 125

Ala Gly Gln Leu Leu Tyr Tyr Ser Xaa Leu
 130 135

<210> 324

<211> 124

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (66)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (102)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (104)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (106)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (109)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (111)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE
 <222> (114)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <220>
 <221> SITE
 <222> (115)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <220>
 <221> SITE
 <222> (122)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <400> 324
 Met Ala Ser Pro Ala Pro Ala Cys Leu Gly Ser Leu Leu Ser Trp Thr
 1 5 10 15
 Val Cys Gly Trp Gly Glu Val Val Ser Gly Pro Pro Cys Ala Val Ser
 20 25 30
 Ala Trp Gly Cys Ser Trp Ala Thr Trp Val Thr Pro Ser Val Val Val
 35 40 45
 Gln Leu Ala Pro Ser Gly Ala Val Gln Thr Pro Leu Ser Pro Glu Leu
 50 55 60
 Leu Xaa Ile Ser Phe Gln Leu His Ala Ala Pro Leu Gly Gln Phe Tyr
 65 70 75 80
 Phe Pro Ile Leu Gln Met Gly Lys Glu Lys Leu Arg Leu Arg Asn Met
 85 90 95
 Pro Lys Glu Ala Pro Xaa Pro Xaa Phe Xaa Leu Phe Xaa Leu Xaa Leu
 100 105 110
 Arg Xaa Xaa Leu Cys His Pro Gly Trp Xaa Ala Gly
 115 120

<210> 325
 <211> 82
 <212> PRT
 <213> Homo sapiens

 <220>
 <221> SITE
 <222> (63)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <220>
 <221> SITE
 <222> (75)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <220>
 <221> SITE
 <222> (76)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <220>
 <221> SITE
 <222> (77)
 <223> Xaa equals any of the naturally occurring L-amino acids

182

<400> 325

Met Gly Gln Leu Cys His Ser Pro Ser Cys Leu Pro Ser Gly Ala Phe
 1 5 10 15
 Cys Leu Leu Leu Ser Ser Val Leu Gly Ile Ile Val Leu Asn Ser Thr
 20 25 30
 Asp Thr Ile Ser Ser Ser His Pro Pro Leu Ser Ser Asn Leu Pro Ser
 35 40 45
 Trp Gly Tyr Thr Thr Thr Lys Ala His Leu Ser Leu Gly Leu Xaa Gly
 50 55 60
 Phe Ala Gly Lys Glu Asn Met Lys Glu Leu Xaa Xaa Xaa Ser Ser Arg
 65 70 75 80
 Ser Phe

<210> 326

<211> 248

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (51)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 326

Met Thr Leu Leu Ser Leu Leu Gly Arg Ile Met Arg Tyr Phe Leu Leu
 1 5 10 15
 Arg Pro Glu Thr Leu Phe Leu Leu Cys Ile Ser Leu Ala Leu Trp Ser
 20 25 30
 Tyr Phe Phe His Thr Asp Glu Val Lys Thr Ile Val Lys Ser Ser Arg
 35 40 45
 Asp Ala Xaa Lys Met Val Lys Gly Lys Val Ala Glu Ile Met Gln Asn
 50 55 60
 Asp Arg Leu Gly Gly Leu Asp Val Leu Glu Ala Glu Phe Ser Lys Thr
 65 70 75 80
 Trp Glu Phe Lys Asn His Asn Val Ala Val Tyr Ser Ile Gln Gly Arg
 85 90 95
 Arg Asp His Met Glu Asp Arg Phe Glu Val Leu Thr Asp Leu Ala Asn
 100 105 110
 Lys Thr His Pro Ser Ile Phe Gly Ile Phe Asp Gly His Gly Gly Glu
 115 120 125
 Thr Ala Ala Glu Tyr Val Lys Ser Arg Leu Pro Glu Ala Leu Lys Gln
 130 135 140
 His Leu Gln Asp Tyr Glu Lys Asp Lys Glu Asn Ser Val Leu Ser Tyr
 145 150 155 160
 Gln Thr Ile Leu Glu Gln Gln Ile Leu Ser Ile Asp Arg Glu Met Leu
 165 170 175
 Glu Lys Leu Thr Val Ser Tyr Asp Glu Ala Gly Thr Thr Cys Leu Ile

183

| | | |
|---|-----|-----|
| 180 | 185 | 190 |
| Ala Leu Leu Ser Asp Lys Asp Leu Thr Val Ala Asn Val Gly Asp Ser | | |
| 195 | 200 | 205 |
| Arg Gly Val Leu Cys Asp Lys Asp Gly Asn Ala Ile Pro Leu Ser His | | |
| 210 | 215 | 220 |
| Asp His Lys Pro Tyr Gln Leu Lys Glu Arg Lys Arg Ile Lys Arg Ala | | |
| 225 | 230 | 235 |
| 240 | | |
| Gly Gly Phe Ile Ser Phe Asn Gly | | |
| 245 | | |

<210> 327
 <211> 27
 <212> PRT
 <213> Homo sapiens

<400> 327
 Phe Leu Ile Ala Leu Asp Leu Leu Asn Val Phe Cys Leu Leu Leu Ser
 1 5 10 15
 Val Phe Ser Leu Glu Ile Glu Cys Lys Pro Tyr
 20 25

<210> 328
 <211> 51
 <212> PRT
 <213> Homo sapiens

<400> 328
 Met Lys Ser Lys Phe Cys Phe Ala Ser Pro Met Arg Leu Pro Lys Ala
 1 5 10 15
 Leu Leu Ala Phe Ser Ala Cys Trp Gln Leu Leu Ser Ala Trp Leu Leu
 20 25 30
 His Leu Ser Pro His Thr Ala Tyr Lys Ser Glu Lys Val Ser Arg Ile
 35 40 45
 Lys Ala Lys
 50

<210> 329
 <211> 33
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (20)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 329
 Met Pro Asn Ser Leu Leu Gly Val Phe Phe Cys Phe Val Leu Phe Cys
 1 5 10 15
 Phe Val Leu Xaa Cys Leu Ile Gln Ser Phe Thr Leu Ser Pro Arg Leu
 20 25 30

Glu

<210> 330
 <211> 99
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (4)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (9)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (16)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (86)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 330
 Gln Lys Ala Xaa Trp Ser Gln Leu Xaa Pro Ile Tyr Leu Thr Val Xaa
 1 5 10 15
 Ile Phe Gln Arg Gln Phe Gln Gly Tyr Tyr Ser His Asp Ser Thr His
 20 25 30
 Pro Gln Gly Val Arg Phe Ser Leu Cys Lys Cys Ile Met Thr Phe Tyr
 35 40 45
 Asn Thr Pro Cys His Ala Leu Phe Tyr Pro Ala Arg Ile Gly Val Trp
 50 55 60
 Pro Gln Leu Val Pro Thr Ser Ser Thr Ala Ile Thr Ser Ser Ser Ser
 65 70 75 80
 Ala Pro Ser Val Val Xaa Glu Pro Leu Val Ser Ser Glu Met His Met
 85 90 95

Leu Lys Ser

<210> 331
 <211> 35
 <212> PRT
 <213> Homo sapiens

<400> 331
 Met Cys His His Ala Gln Leu Ile Phe Val Leu Leu Val Glu Thr Gly
 1 5 10 15
 Phe Cys His Val Gly Gln Ala Gly Leu Glu Leu Leu Thr Ser His Asp
 20 25 30

185

Leu Arg Thr
35

<210> 332
<211> 262
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (154)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 332
His Gly Pro Pro Glu Gly Ala Val Gly Cys Gln Arg Glu Gln Gln Arg
1 5 10 15

Gln Ala Ala Ala Gln Pro Arg Gln His Gln Ala Ile Arg Ser Val Gly
20 25 30

Arg Gln Pro Val Val Cys Cys Pro Gln Thr Leu Asp Ala Gly Leu Gly
35 40 45

Pro Gly His Ala Ala Val Ala Arg Pro Leu Leu Arg Pro Leu Gln Val
50 55 60

Gly Glu Ala Glu Cys Gly His Gly Gln Gln Gly Gly Gln Asp Pro Ala
65 70 75 80

Gly Ser Ala His Gly Pro Gly Val Leu Gly Ser Gln Val Ala Ser Gly
85 90 95

Glu Glu Gly Val His Asp Ala Gln Val Ala Val Glu Ala Asp Ala Gly
100 105 110

Asp Glu Asp Asp Ala Ala Gln Gln Val Ala Gly Glu Glu Glu Ala Leu
115 120 125

Gln Ala Ala Arg Gly Leu Pro Ile Ala Pro Val Leu Gly Gly Ile Glu
130 135 140

Val Gly Gly Gln Arg Gly Gln Arg Gln Xaa Ala Glu Gln Val Ala Asp
145 150 155 160

Cys Gln Leu Asp Arg Glu Asp His Gly Gly Val Pro Trp Ala Leu Leu
165 170 175

Pro Asp Ala Glu Ala Val Gln Gly Gln Ala Ile Ala Gly His Gly His
180 185 190

Gln Glu Leu Asn His Gln Tyr Gly Pro Gln Glu Val Pro Leu Glu Pro
195 200 205

Thr Glu Phe Val Val Gly Ser Cys Gln Glu Val Gly Arg Ala Gly Leu
210 215 220

Gly Thr Arg Asp Val Gly Cys His Ala Pro Val Pro Ile Leu Ser Leu
225 230 235 240

Cys Leu Leu Pro Ser Ser Pro Ala Pro Pro Pro Val Thr Ser Gly Leu
245 250 255

Val Gly Pro Ala Pro Ala

186

260

<210> 333
 <211> 82
 <212> PRT
 <213> Homo sapiens

<400> 333
 Met Leu Thr Asn Arg Ala Pro Ser Ser Phe Val Trp Phe Leu Cys Leu
 1 5 10 15
 Ala Cys His Leu Pro Ser Cys Pro Ser Ala Thr Glu Glu Phe Ala Val
 20 25 30
 Phe Ile Pro Lys Tyr His Ser Ser Arg Met Gly Ala Ala Pro Cys His
 35 40 45
 Val Leu Gly His Gly Gly Ile Lys Gly Asn Thr Cys Gln Asp Asn Ala
 50 55 60
 Gly Tyr Asp Phe Cys Arg Pro Leu Gly Leu Ala Ser Phe Leu Lys Arg
 65 70 75 80
 Gln Asp

<210> 334
 <211> 587
 <212> PRT
 <213> Homo sapiens

<400> 334
 Met Arg Pro Arg Gly Leu Pro Pro Leu Leu Val Val Leu Leu Gly Cys
 1 5 10 15
 Trp Ala Ser Val Ser Ala Gln Thr Asp Ala Thr Pro Ala Val Thr Thr
 20 25 30
 Glu Gly Leu Asn Ser Thr Glu Ala Ala Leu Ala Thr Phe Gly Thr Phe
 35 40 45
 Pro Ser Thr Arg Pro Pro Gly Thr Pro Arg Ala Pro Gly Pro Ser Ser
 50 55 60
 Gly Pro Arg Pro Thr Pro Val Thr Asp Val Ala Val Leu Cys Val Cys
 65 70 75 80
 Asp Leu Ser Pro Ala Gln Cys Asp Ile Asn Cys Cys Cys Asp Pro Asp
 85 90 95
 Cys Ser Ser Val Asp Phe Ser Val Phe Ser Ala Cys Ser Val Pro Val
 100 105 110
 Val Thr Gly Asp Ser Gln Phe Cys Ser Gln Lys Ala Val Ile Tyr Ser
 115 120 125
 Leu Asn Phe Thr Ala Asn Pro Pro Gln Arg Val Phe Glu Leu Val Asp
 130 135 140
 Gln Ile Asn Pro Ser Ile Phe Cys Ile His Ile Thr Asn Tyr Lys Pro
 145 150 155 160

187

Ala Leu Ser Phe Ile Asn Pro Glu Val Pro Asp Glu Asn Asn Phe Asp
 165 170 175
 Thr Leu Met Lys Thr Ser Asp Gly Phe Thr Leu Asn Ala Glu Ser Tyr
 180 185 190
 Val Ser Phe Thr Thr Lys Leu Asp Ile Pro Thr Ala Ala Lys Tyr Glu
 195 200 205
 Tyr Gly Val Pro Leu Gln Thr Ser Asp Ser Phe Leu Arg Phe Pro Ser
 210 215 220
 Ser Leu Thr Ser Ser Leu Cys Thr Asp Asn Asn Pro Ala Ala Phe Leu
 225 230 235 240
 Val Asn Gln Ala Val Lys Cys Thr Arg Lys Ile Asn Leu Glu Gln Cys
 245 250 255
 Glu Glu Ile Glu Ala Leu Ser Met Ala Phe Tyr Ser Ser Pro Glu Ile
 260 265 270
 Leu Arg Val Pro Asp Ser Arg Lys Lys Val Pro Ile Thr Val Gln Ser
 275 280 285
 Ile Val Ile Gln Ser Leu Asn Lys Thr Leu Thr Arg Arg Glu Asp Thr
 290 295 300
 Asp Val Leu Gln Pro Thr Leu Val Asn Ala Gly His Phe Ser Leu Cys
 305 310 315 320
 Val Asn Val Val Leu Glu Val Lys Tyr Ser Leu Thr Tyr Thr Asp Ala
 325 330 335
 Gly Glu Val Thr Lys Ala Asp Leu Ser Phe Val Leu Gly Thr Val Ser
 340 345 350
 Ser Val Val Val Pro Leu Gln Gln Lys Phe Glu Ile His Phe Leu Gln
 355 360 365
 Glu Asn Thr Gln Pro Val Pro Leu Ser Gly Asn Pro Gly Tyr Val Val
 370 375 380
 Gly Leu Pro Leu Ala Ala Gly Phe Gln Pro His Lys Gly Ser Gly Ile
 385 390 395 400
 Ile Gln Thr Thr Asn Arg Tyr Gly Gln Leu Thr Ile Leu His Ser Thr
 405 410 415
 Thr Glu Gln Asp Cys Leu Ala Leu Glu Gly Val Arg Thr Pro Val Leu
 420 425 430
 Phe Gly Tyr Thr Met Gln Ser Gly Cys Lys Leu Arg Leu Thr Gly Ala
 435 440 445
 Leu Pro Cys Gln Leu Val Ala Gln Lys Val Lys Ser Leu Leu Trp Gly
 450 455 460
 Gln Gly Phe Pro Asp Tyr Val Ala Pro Phe Gly Asn Ser Gln Ala Gln
 465 470 475 480
 Asp Met Leu Asp Trp Val Pro Ile His Phe Ile Thr Gln Ser Phe Asn
 485 490 495
 Arg Lys Asp Ser Cys Gln Leu Pro Gly Ala Leu Val Ile Glu Val Lys
 500 505 510

188

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Trp | Thr | Lys | Tyr | Gly | Ser | Leu | Leu | Asn | Pro | Gln | Ala | Lys | Ile | Val | Asn |
| | | 515 | | | | | 520 | | | | | 525 | | | |
| Val | Thr | Ala | Asn | Leu | Ile | Ser | Ser | Ser | Phe | Pro | Glu | Ala | Asn | Ser | Gly |
| | 530 | | | | | 535 | | | | | 540 | | | | |
| Asn | Glu | Arg | Thr | Ile | Leu | Ile | Ser | Thr | Ala | Val | Thr | Phe | Val | Asp | Val |
| 545 | | | | | 550 | | | | | 555 | | | | | 560 |
| Ser | Ala | Pro | Ala | Glu | Ala | Gly | Phe | Arg | Ala | Pro | Pro | Ala | Ile | Asn | Ala |
| | | | | 565 | | | | | 570 | | | | | 575 | |
| Arg | Leu | Pro | Phe | Asn | Phe | Phe | Phe | Pro | Phe | Val | | | | | |
| | | | 580 | | | | | 585 | | | | | | | |

```
<210> 335
<211> 337
<212> PRT
<213> Homo sapiens
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```
<220>
<221> SITE
<222> (173)
<223> Xaa equals any of the naturally occurring L-amino acids
```

```
<220>
<221> SITE
<222> (255)
<223> Xaa equals any of the naturally occurring L-amino acids
```

```
<220>
<221> SITE
<222> (320)
<223> Xaa equals any of the naturally occurring L-amino acids
```

| | | | | | | | | | | | | | | | |
|-----------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| <400> 335 | | | | | | | | | | | | | | | |
| Met | Gly | Leu | Ile | Val | Val | Leu | Leu | Phe | Pro | Asn | Leu | Cys | Met | Cys | Thr |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |
| Phe | His | Ala | Gly | Gly | Phe | Gln | Cys | Val | Leu | Trp | Met | Ala | Gly | Leu | Lys |
| | | | 20 | | | | | 25 | | | | | 30 | | |
| Arg | Arg | Val | Pro | Leu | His | Ser | Leu | Arg | Tyr | Phe | Ile | Ser | Met | Val | Gly |
| | | 35 | | | | | 40 | | | | | 45 | | | |
| Leu | Phe | Ser | Lys | Pro | Gly | Leu | Leu | Pro | Trp | Tyr | Ala | Arg | Asn | Pro | Pro |
| | 50 | | | | | 55 | | | | | 60 | | | | |
| Gly | Trp | Ser | Gln | Leu | Phe | Leu | Gly | Thr | Val | Cys | Lys | Gly | Asp | Phe | Thr |
| 65 | | | | | 70 | | | | | 75 | | | | | 80 |
| Arg | Val | Ile | Ala | Thr | Lys | Cys | Gln | Lys | Gly | Gln | Lys | Ser | Gln | Lys | Lys |
| | | | | 85 | | | | | 90 | | | | | 95 | |
| Pro | Ser | His | Leu | Gly | Pro | Leu | Asp | Gly | Ser | Trp | Gln | Glu | Arg | Leu | Ala |
| | | | | | | | | | | | | | | | |
| | | | 100 | | | | | 105 | | | | | 110 | | |
| Asp | Val | Val | Thr | Pro | Leu | Trp | Arg | Leu | Ser | Tyr | Glu | Glu | Gln | Leu | Lys |
| | | 115 | | | | | 120 | | | | | 125 | | | |
| Val | Lys | Phe | Ala | Ala | Gln | Lys | Lys | Ile | Leu | Gln | Arg | Leu | Glu | Ser | Tyr |
| | 130 | | | | | 135 | | | | | 140 | | | | |

189

Ile Gln Met Leu Asn Gly Val Ser Val Thr Thr Ala Val Pro Lys Ser
 145 150 155 160
 Glu Arg Leu Ser Cys Leu Leu His Pro Ile Ile Pro Xaa Pro Val Ile
 165 170 175
 Asn Gly Tyr Arg Asn Lys Ser Thr Phe Ser Val Asn Arg Gly Pro Asp
 180 185 190
 Gly Asn Pro Lys Thr Val Gly Phe Tyr Leu Gly Thr Trp Arg Asp Gly
 195 200 205
 Asn Val Val Cys Val Gln Ser Asn His Leu Lys Asn Ile Pro Glu Lys
 210 215 220
 His Ser Gln Val Ala Gln Tyr Tyr Glu Val Phe Leu Arg Gln Ser Pro
 225 230 235 240
 Leu Glu Pro Cys Leu Val Phe His Glu Gly Gly Tyr Trp Arg Xaa Leu
 245 250 255
 Thr Val Arg Thr Asn Ser Gln Gly His Thr Met Ala Ile Ile Thr Phe
 260 265 270
 His Pro Gln Lys Leu Ser Gln Glu Glu Leu His Val Gln Lys Glu Ile
 275 280 285
 Val Lys Glu Phe Phe Ile Lys Arg Ser Trp Ser Ser Leu Trp Leu Asp
 290 295 300
 Leu Thr Leu Leu Pro Gly Lys Tyr His Asp Pro Leu Gln Pro Ser Xaa
 305 310 315 320
 Val Ser Leu Ser Ser Phe Cys Leu Gly Asn Leu His Leu Leu Lys Asn
 325 330 335

Phe

<210> 336
 <211> 125
 <212> PRT
 <213> Homo sapiens

<400> 336
 Met Ser Asn Thr Asn Gly Ser Ala Ile Thr Glu Phe Ile Leu Leu Gly
 1 5 10 15
 Leu Thr Asp Cys Pro Glu Leu Gln Ser Leu Leu Phe Val Leu Phe Leu
 20 25 30
 Val Val Tyr Leu Val Thr Leu Leu Gly Asn Leu Gly Met Ile Met Leu
 35 40 45
 Met Arg Leu Asp Ser Arg Leu His Thr Pro Met Tyr Phe Phe Leu Thr
 50 55 60
 Asn Leu Ala Phe Val Asp Leu Cys Tyr Thr Ser Asn Ala Thr Pro Gln
 65 70 75 80
 Met Ser Thr Asn Ile Val Ser Glu Lys Thr Ile Ser Phe Ala Gly Cys
 85 90 95
 Phe Thr Gln Cys Tyr Ile Phe Ile Ala Leu Leu Leu Thr Glu Phe Tyr

190

100 105 110
 Met Leu Ala Ala Met Ala Tyr Asp Arg Tyr Val Ala Ile
 115 120 125

 <210> 337
 <211> 132
 <212> PRT
 <213> Homo sapiens

 <400> 337
 Met Arg Leu Leu Val Leu Ser Ser Leu Leu Cys Ile Leu Leu Leu Cys
 1 5 10 15
 Phe Ser Ile Phe Ser Thr Glu Gly Lys Arg Arg Pro Ala Lys Ala Trp
 20 25 30
 Ser Gly Arg Arg Thr Arg Leu Cys Cys His Arg Val Pro Ser Pro Asn
 35 40 45
 Ser Thr Asn Leu Lys Ala Phe Thr Ala Val Ser Cys Asn Val Gly Gly
 50 55 60
 Leu His Leu Gly Leu Gln Gly Pro Trp Glu Ser Ser Arg Thr Pro Arg
 65 70 75 80
 Pro Cys Leu Asn Cys Ala Ile Asn Phe Gln Ser Tyr His Glu Pro Thr
 85 90 95
 Ser Pro His Arg Ala Ser Val Ala Thr Met Trp Ala Ser Pro Val Gln
 100 105 110
 Thr Thr Glu His Ser Thr Met Thr Gly His Ser Tyr Lys Ser Arg Asp
 115 120 125

 His Gln Ser Cys
 130

<210> 338
 <211> 81
 <212> PRT
 <213> Homo sapiens

 <400> 338
 Met Arg Leu Leu Val Leu Ser Ser Leu Leu Cys Ile Leu Leu Leu Cys
 1 5 10 15
 Phe Ser Ile Phe Ser Thr Glu Gly Lys Arg Arg Pro Ala Lys Ala Trp
 20 25 30
 Ser Gly Arg Arg Thr Arg Leu Cys Cys His Arg Val Pro Ser Pro Asn
 35 40 45
 Ser Thr Asn Leu Lys Gly His His Val Arg Leu Cys Lys Pro Cys Lys
 50 55 60
 Leu Glu Pro Glu Pro Arg Leu Trp Val Val Pro Gly Ala Leu Pro Gln
 65 70 75 80
 Val

<210> 339
 <211> 173
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (128)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (153)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (160)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (166)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 339
 Met Ser Gly Leu Ser Arg Pro Leu Leu Leu Ala Val Gly Cys Leu Ala
 1 5 10 15
 Ala Leu Cys Val Ile Thr Ala Ala Gly Asn Thr Thr Leu Ala Pro Asn
 20 25 30
 Val Thr Thr Ala Ser Ser Pro Pro Pro Thr Thr Thr Thr Val Pro Val
 35 40 45
 Ser Pro Thr Thr Leu Ser Pro Leu Pro Val Thr Thr Pro Ala Pro Asp
 50 55 60
 Ile Cys Gly Ser Arg Asn Ser Cys Val Ser Cys Val Asp Gly Asn Ala
 65 70 75 80
 Thr Cys Phe Trp Ile Glu Cys Lys Gly Lys Ser Tyr Cys Ser Asp Asn
 85 90 95
 Ser Thr Ala Gly Asp Cys Lys Val Val Asn Thr Thr Gly Phe Cys Ser
 100 105 110
 Ala Lys Thr Thr Thr Leu Pro Ser Thr Thr Thr Thr Ser Thr Thr Xaa
 115 120 125
 Thr Thr Ser Gly Thr Thr Asn Thr Thr Leu Ser Pro Thr Ile Gln Pro
 130 135 140
 Thr Arg Lys Ser Thr Phe Asp Ala Xaa Gln Phe His Trp Arg Asn Xaa
 145 150 155 160
 Pro Cys Leu Gly Val Xaa Ala Val Ile Phe Phe Leu Tyr
 165 170

<210> 340
 <211> 91
 <212> PRT

192

<213> Homo sapiens

<400> 340

```

Met Ser Arg Cys Thr Trp Pro Ser Phe Ser Phe Phe Leu Ser Ser Phe
 1           5           10           15
Leu Ser Phe Phe Arg Trp Ser Leu Ala Leu Ser Ala Arg Leu Glu Gly
           20           25           30
Ser Gly Val Ile Leu Ala His Cys Asn Leu Arg Leu Pro Gly Ser Ser
           35           40           45
Asp Ser Pro Ala Ser Ala Ser Gln Ser Ala Gly Ile Thr Gly Met Ser
           50           55           60
Arg Cys Ala Asp Val His Leu Val Ser Ile Ile Thr Lys Ala His Leu
           65           70           75           80
Val Ser Trp Pro Leu Gln Met Asn Ile Leu Pro
           85           90

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<210> 341

<211> 139

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (23)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 341

```

Pro Pro Arg Pro Gly Cys Pro Val Pro Gln Trp Gly Cys Ser Ser Ala
 1           5           10           15
Trp Pro Cys Pro Ser Gln Xaa His His His Pro Ala Asn Asp Cys Gln
           20           25           30
Thr Val Gly Arg His Ser Pro Leu Asp Leu Asn Leu Lys Ser Pro Ser
           35           40           45
Leu Pro Trp Leu Asp Pro Gly Asp Pro Phe Ala Leu Pro Ser Ala Pro
           50           55           60
Ser Pro Thr Asp Leu Leu Cys Asp Leu Arg Pro Val Cys Arg Pro Leu
           65           70           75           80
Trp Ala Ser Val Phe Pro Ala Met Lys Thr Ala Ile Ser Gln Ser Cys
           85           90           95
Val Lys Gln Lys Arg Lys Ala Gly Gly Arg Pro Trp Ala Asn Gly Arg
           100           105           110
Ala Leu Val Ile Ile Asn Ile Val Ala Ala Val Val Leu Leu Leu Leu
           115           120           125
Ile Asn Ile His Ile Ile Tyr Phe Ile Leu Thr
           130           135

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<210> 342

<211> 86

<212> PRT

193

<213> Homo sapiens

<220>

<221> SITE

<222> (34)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (63)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (71)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (82)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 342

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Val | Phe | Pro | Leu | Leu | Cys | Val | Phe | Val | Leu | Ile | Ser | Ser | Ser | Leu |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ala | Gly | Glu | Glu | Ala | Ala | Gly | Leu | Arg | Val | Gln | Lys | Leu | Trp | Pro | Ala |
| | | | 20 | | | | 25 | | | | | | 30 | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Xaa | Leu | Ser | His | Leu | Pro | Val | Cys | Trp | Phe | His | Cys | Ser | Gly | Ile |
| | | 35 | | | | 40 | | | | | | 45 | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Trp | Ser | Glu | Val | Ile | Glu | Leu | Lys | Val | Gly | Trp | Glu | Gly | His | Xaa | Leu |
| | 50 | | | | | 55 | | | | | 60 | | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Pro | Trp | Gln | Ala | His | Val | Xaa | Glu | Phe | Lys | Val | Val | Glu | His | Leu | Ile |
| 65 | | | | | 70 | | | | | 75 | | | | | 80 |

| | | | | | |
|-----|-----|-----|-----|-----|-----|
| Ser | Xaa | Met | Gly | Ala | Gly |
| | | | | 85 | |

<210> 343

<211> 118

<212> PRT

<213> Homo sapiens

<400> 343

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | His | Cys | His | Cys | Arg | Val | Trp | Gly | Phe | Arg | Trp | Phe | Leu | Gly | Asp |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Trp | Glu | Leu | Leu | Val | Cys | Met | Cys | Trp | Val | His | Ala | Ser | Gly | Ser | Gln |
| | | | 20 | | | | | 25 | | | | | 30 | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Pro | Gln | Ala | Arg | Thr | Gly | Asn | Pro | Phe | Pro | Ser | Lys | Ala | Ile | Gly |
| | | 35 | | | | | 40 | | | | | 45 | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Ala | Ser | Leu | Glu | Ser | Phe | Ala | Lys | Ser | Pro | Arg | Gln | Asn | Pro | Arg |
| | 50 | | | | | 55 | | | | | 60 | | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Gln | Asp | His | Phe | His | Gly | Ala | His | Val | Phe | Leu | Phe | Cys | Arg | Asn |
| 65 | | | | | 70 | | | | 75 | | | | | | 80 |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Phe | Phe | Leu | Thr | Ser | Thr | His | His | Asn | Ser | Glu | Gly | His | Val | Ser | Ser |
| | | | | 85 | | | | | 90 | | | | | 95 | |

Phe Leu Asp His Tyr Ser Glu Val Leu Gln Leu Tyr Ser Ser Gln Ser
 100 105 110

Gly Leu Gly Leu Leu Gly
 115

<210> 344

<211> 365

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (189)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (253)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (365)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 344

Met Phe Gly Thr Leu Leu Leu Tyr Cys Phe Phe Leu Ala Thr Val Pro
 1 5 10 15

Ala Leu Ala Glu Thr Gly Gly Glu Arg Gln Leu Ser Pro Glu Lys Ser
 20 25 30

Glu Ile Trp Gly Pro Gly Leu Lys Ala Asp Val Val Leu Pro Ala Arg
 35 40 45

Tyr Phe Tyr Ile Gln Ala Val Asp Thr Ser Gly Asn Lys Phe Thr Ser
 50 55 60

Ser Pro Gly Glu Lys Val Phe Gln Val Lys Val Ser Ala Pro Glu Glu
 65 70 75 80

Gln Phe Thr Arg Val Gly Val Gln Val Leu Asp Arg Lys Asp Gly Ser
 85 90 95

Phe Ile Val Arg Tyr Arg Met Tyr Ala Ser Tyr Lys Asn Leu Lys Val
 100 105 110

Glu Val Lys Phe Gln Gly Gln His Val Ala Lys Ser Pro Tyr Ile Leu
 115 120 125

Lys Gly Pro Val Tyr His Glu Asn Cys Asp Cys Pro Leu Gln Asp Ser
 130 135 140

Ala Ala Trp Leu Arg Glu Met Asn Cys Pro Glu Thr Ile Ala Gln Ile
 145 150 155 160

Gln Arg Asp Leu Ala His Phe Pro Ala Val Asp Pro Glu Lys Ile Ala
 165 170 175

Val Glu Ile Pro Lys Arg Phe Gly Gln Arg Gln Ser Xaa Cys His Tyr
 180 185 190

195

Thr Leu Lys Asp Asn Lys Val Tyr Ile Lys Thr His Gly Glu His Val
 195 200 205
 Gly Phe Arg Ile Phe Met Asp Ala Ile Leu Leu Ser Leu Thr Arg Lys
 210 215 220
 Val Lys Met Pro Asp Val Glu Leu Phe Val Asn Leu Gly Asp Trp Pro
 225 230 235 240
 Leu Glu Lys Lys Lys Ser Asn Ser Asn Ile His Pro Xaa Phe Ser Trp
 245 250 255
 Cys Gly Ser Thr Asp Ser Lys Asp Ile Val Met Pro Thr Tyr Asp Leu
 260 265 270
 Thr Asp Ser Val Leu Glu Thr Met Gly Arg Val Ser Leu Asp Met Met
 275 280 285
 Ser Val Gln Ala Asn Thr Gly Pro Pro Trp Glu Ser Lys Asn Ser Thr
 290 295 300
 Ala Val Trp Arg Gly Arg Asp Ser Arg Lys Glu Arg Leu Glu Leu Val
 305 310 315 320
 Lys Leu Ser Arg Lys His Pro Glu Leu Ile Asp Ala Ala Phe Thr Asn
 325 330 335
 Phe Phe Phe Phe Lys His Asp Glu Asn Leu Tyr Gly Pro Ile Val Asn
 340 345 350
 Ile Phe His Phe Leu Ile Ser Ser Ser Ile Ser Ile Xaa
 355 360 365

<210> 345

<211> 62

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (3)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 345

Met Thr Xaa Gln Leu Leu Phe Asn Ser Phe Leu Leu Ser Ser Val Ser
 1 5 10 15
 Gln Ile Arg Asp Gln Ile Ala Met Arg Glu Ser Val Trp Ser Gly Ser
 20 25 30
 Ile Ser Arg Gln Lys Glu Leu Val Thr Leu Trp Ile Ile Cys Leu Trp
 35 40 45
 Phe Arg His Leu Pro Leu Val Leu Ala Val Gly Asp Gly Trp
 50 55 60

<210> 346

<211> 18

<212> PRT

<213> Homo sapiens

196

<220>

<221> SITE

<222> (8)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 346

Cys Pro Ala Leu Phe Asn Ile Xaa Phe Glu Asn Ser Ile Leu Tyr Cys
 1 5 10 15

Gln Ile

<210> 347

<211> 306

<212> PRT

<213> Homo sapiens

<400> 347

Met Gly His Arg Thr Leu Val Leu Pro Trp Val Leu Leu Thr Leu Cys
 1 5 10 15

Val Thr Ala Gly Thr Pro Glu Val Trp Val Gln Val Arg Met Glu Ala
 20 25 30

Thr Glu Leu Ser Ser Phe Thr Ile Arg Cys Gly Phe Leu Gly Ser Gly
 35 40 45

Ser Ile Ser Leu Val Thr Val Ser Trp Gly Gly Pro Asp Gly Ala Gly
 50 55 60

Gly Thr Thr Leu Ala Val Leu His Pro Glu Arg Gly Ile Arg Gln Trp
 65 70 75 80

Ala Pro Ala Arg Gln Ala Arg Trp Glu Thr Gln Ser Ser Ile Ser Leu
 85 90 95

Ile Leu Glu Gly Ser Gly Ala Ser Ser Pro Cys Ala Asn Thr Thr Phe
 100 105 110

Cys Cys Lys Phe Ala Ser Phe Pro Glu Gly Ser Trp Glu Ala Cys Gly
 115 120 125

Ser Leu Pro Pro Ser Ser Asp Pro Gly Leu Ser Ala Pro Pro Thr Pro
 130 135 140

Ala Pro Ile Leu Arg Ala Asp Leu Ala Gly Ile Leu Gly Val Ser Gly
 145 150 155 160

Val Leu Leu Phe Gly Cys Val Tyr Leu Leu His Leu Leu Arg Arg His
 165 170 175

Lys His Arg Pro Ala Pro Arg Leu Gln Pro Ser Arg Thr Ser Pro Gln
 180 185 190

Ala Pro Arg Ala Arg Ala Trp Ala Pro Ser Gln Ala Ser Gln Ala Ala
 195 200 205

Leu His Val Pro Tyr Ala Thr Ile Asn Thr Ser Cys Arg Pro Ala Thr
 210 215 220

Leu Asp Thr Ala His Pro His Gly Gly Pro Ser Trp Trp Ala Ser Leu
 225 230 235 240

Pro Thr His Ala Ala His Arg Pro Gln Gly Pro Ala Ala Trp Ala Ser

245

250

255

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<210> 348
<211> 106
<212> PRT
<213> Homo sapiens
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<220>
<221> SITE
<222> (94)
<223> Xaa equals any of the naturally occurring L-amino acids
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<220>
<221> SITE
<222> (102)
<223> Xaa equals any of the naturally occurring L-amino acids
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<220>
<221> SITE
<222> (106)
<223> Xaa equals any of the naturally occurring L-amino acids

```

<400> 348
Met Gly Trp Ser Arg Gly Glu Gly Gln Gln Gly Trp Leu Ala Ala Ala
1 5 10 15

Leu Cys Gly Trp Thr Arg Leu Gly Lys Ala Glu Gly Ser Glu Gly Trp
20 25 30

Ala Thr Leu Glu Gly Cys Gln Val Pro Ser Leu Leu Gln Gly Asn Glu
35 40 45

Gly Gly Ala Ala Leu Asn Arg His Met Pro Lys Gln Gly Ile Asp Ala
50 55 60

Trp Ile Lys Leu Ala Thr Thr Arg Arg Ser Leu Phe Gly Ile Phe Gln
65 70 75 80

Ile Leu Arg His Pro Ser Cys Asp Asp Gly Val Glu Arg Xaa Thr Gly
85 90 95

Pro Leu Glu Phe Cys Xaa Leu His Arg Xaa
100 105

```
<210> 349
<211> 137
<212> PRT
<213> Homo sapiens
```

<400> 349

198

Ala Leu Met Ser Arg Gln Arg Gly Pro Gly Glu Asn Pro Ala Pro Ser
 1 5 10 15
 Val Ile Pro Leu His Phe Leu Pro Ser Phe Leu Leu Cys Leu Ala Lys
 20 25 30
 Glu Gly Ser Ser Leu Gly Cys Pro Tyr Asn Ala Pro Gly Pro Arg Leu
 35 40 45
 Ser Asn Lys Lys Pro Glu Pro Cys Gly Pro Val Ala Arg Ala Ser Ser
 50 55 60
 Gly Arg Leu Pro Leu Leu Cys Leu Gly Pro Leu Ser Pro Ala Ser Arg
 65 70 75 80
 Ala Arg Val Arg Leu Gln Ala Ser Gly His Cys Pro Gly Cys Asp Gly
 85 90 95
 Thr Lys Ala Gly Gly Ala Pro Gly Thr Thr Gln Leu Gly Phe Pro Pro
 100 105 110
 Gly Phe Pro Ala Gly Val Ser Gly Ser Phe Ser Pro Ala Leu Leu Gly
 115 120 125
 Val Cys Arg Asn Trp Pro Cys Ser Pro
 130 135

<210> 350

<211> 102

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (11)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (56)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 350

Glu Thr Arg Thr Leu Gln Pro Pro Gly Pro Xaa Cys Val Cys Arg Pro
 1 5 10 15
 Val Ala Thr Val Arg Ala Val Met Ala Pro Arg Gln Val Glu His Gln
 20 25 30
 Val Pro His Ser Trp Ala Ser His Gln Ala Phe Pro Arg Gly Ser Gln
 35 40 45
 Gly Ala Ser Pro Gln Arg Cys Xaa Glu Ser Ala Gly Thr Gly Leu Val
 50 55 60
 Leu Leu Ser Pro Ser Leu His Thr Val Leu Gly Glu Asp Gly Cys Gly
 65 70 75 80
 Arg Cys Pro Cys Arg Glu Val Thr Val Glu Val Ala Val Ala Cys Ser
 85 90 95
 His Leu Trp Glu Glu Lys
 100

199

<210> 351
 <211> 133
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (131)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 351
 Met Arg Leu Phe Val Ser Val Thr Val Leu Val Ile Cys Leu Ala Asp
 1 5 10 15
 Leu Glu Glu Glu Ser Glu Ser Trp Asp Asn Ser Glu Ser Glu Glu Glu
 20 25 30
 Glu Lys Ala Pro Val Leu Pro Glu Ser Thr Glu Gly Arg Glu Leu Thr
 35 40 45
 Gln Gly Pro Ala Glu Ser Ser Ser Leu Ser Gly Cys Gly Ser Trp Gln
 50 55 60
 Pro Arg Lys Leu Pro Val Phe Lys Ser Leu Arg His Met Arg Gln Val
 65 70 75 80
 Gly Gly Arg Gly Thr Ala His Gln Glu Leu Arg Arg Arg Ala Asn His
 85 90 95
 Gly Leu Ser Leu Pro Thr Arg Leu Ala Ser Gly Pro Ser Thr Phe Lys
 100 105 110
 Thr Leu Gln Glu Val Thr Asp Ser Leu Leu Gly Gly Trp Leu Arg Ala
 115 120 125
 Gln Gly Xaa Gly Gly
 130

<210> 352
 <211> 136
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (96)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (98)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 352
 Met Ile Leu Leu Ile Ile Leu Trp Ile Leu Arg Glu Ile Gln Ser Ile
 1 5 10 15
 Tyr Ile Ile Gly Ile Phe Arg Asn Pro Phe Tyr Pro Lys Asp Val Gln
 20 25 30
 Thr Val Thr Val Phe Phe Glu Lys Gln Thr Arg Leu Met Lys Ile Gly
 35 40 45



200

```

Ile Val Arg Arg Ile Leu Leu Thr Leu Val Ser Pro Phe Ala Met Ile
  50              55              60
Ala Phe Leu Ser Leu Asp Ser Ser Leu Gln Gly Leu His Ser Val Ser
  65              70              75              80
Val Cys Ile Gly Phe Thr Arg Ala Phe Arg Met Val Trp Gln Asn Xaa
              85              90              95
Glu Xaa Ala Leu Leu Glu Thr Val Ile Val Ser Thr Val His Leu Ile
              100              105              110
Ser Ser Thr Asp Ile Trp Trp Asn Arg Ser Leu Asp Thr Gly Leu Arg
      115              120              125
Leu Leu Leu Val Gly Ile His Thr
  130              135

```

<210> 353

<211> 134

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (45)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (133)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 353

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Met Ile Leu Leu Ile Ile Leu Trp Ile Leu Arg Glu Ile Gln Ser Ile
  1              5              10              15
Tyr Ile Ile Gly Ile Phe Arg Asn Pro Phe Tyr Pro Lys Asp Val Gln
              20              25              30
Thr Val Thr Val Phe Phe Glu Lys Gln Thr Arg Leu Xaa Lys Ile Gly
      35              40              45
Ile Val Arg Arg Ile Leu Leu Thr Leu Val Ser Pro Phe Ala Met Ile
  50              55              60
Ala Phe Leu Ser Leu Asp Ser Ser Leu Gln Gly Leu His Ser Val Ser
  65              70              75              80
Val Cys Ile Gly Phe Thr Arg Ala Phe Arg Met Val Trp Gln Asn Thr
              85              90              95
Glu Asn Ala Leu Leu Glu Thr Val Ile Val Ser Thr Val His Leu Ile
              100              105              110
Ser Ser Thr Asp Ile Trp Trp Asn Arg Ser Leu Asp Thr Gly Gly Thr
      115              120              125
His Phe Val Asn Xaa Val
  130

```

201

<210> 354

<211> 303

<212> PRT

<213> Homo sapiens

<400> 354

Gly Arg Leu Arg Gly Ala Gly Arg Gly Val Gln Arg Ala Met Ala Ala
 1 5 10 15
 Leu Arg Val Leu Leu Ser Cys Ala Arg Gly Pro Leu Arg Pro Pro Val
 20 25 30
 Arg Cys Pro Ala Trp Arg Pro Phe Ala Ser Gly Ala Asn Phe Glu Tyr
 35 40 45
 Ile Ile Ala Glu Lys Arg Gly Lys Asn Asn Thr Val Gly Leu Ile Gln
 50 55 60
 Leu Asn Arg Pro Lys Ala Leu Asn Ala Leu Cys Asp Gly Leu Ile Asp
 65 70 75 80
 Glu Leu Asn Gln Ala Leu Lys Ile Phe Glu Glu Asp Pro Ala Val Gly
 85 90 95
 Ala Ile Val Leu Thr Gly Gly Asp Lys Ala Phe Ala Ala Gly Ala Asp
 100 105 110
 Ile Lys Glu Met Gln Asn Leu Ser Phe Gln Asp Cys Tyr Ser Ser Lys
 115 120 125
 Phe Leu Lys His Trp Asp His Leu Thr Gln Val Lys Lys Pro Val Ile
 130 135 140
 Ala Ala Val Asn Gly Tyr Ala Phe Gly Gly Gly Cys Glu Leu Ala Met
 145 150 155 160
 Met Cys Asp Ile Ile Tyr Ala Gly Glu Lys Ala Gln Phe Ala Gln Pro
 165 170 175
 Glu Ile Leu Ile Gly Thr Ile Pro Gly Ala Gly Gly Thr Gln Arg Leu
 180 185 190
 Thr Arg Ala Val Gly Lys Ser Leu Ala Met Glu Met Val Leu Thr Gly
 195 200 205
 Asp Arg Ile Ser Ala Gln Asp Ala Lys Gln Ala Gly Leu Val Ser Lys
 210 215 220
 Ile Cys Pro Val Glu Thr Leu Val Glu Glu Ala Ile Gln Cys Ala Glu
 225 230 235 240
 Lys Ile Ala Ser Asn Ser Lys Ile Val Val Ala Met Ala Lys Glu Ser
 245 250 255
 Val Asn Ala Ala Phe Glu Met Thr Leu Thr Glu Gly Ser Lys Leu Glu
 260 265 270
 Lys Lys Leu Phe Tyr Ser Thr Phe Ala Thr Asp Asp Arg Lys Glu Gly
 275 280 285
 Met Thr Ala Phe Val Glu Lys Arg Lys Ala Asn Phe Lys Asp Gln
 290 295 300

<210> 355

202

<211> 118
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (62)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 355
 Met Glu Met Ala Ser Ser Ala Gly Ser Trp Leu Ser Gly Cys Leu Ile
 1 5 10 15
 Pro Leu Val Phe Leu Arg Leu Ser Val His Val Ser Gly His Ala Gly
 20 25 30
 Asp Ala Gly Lys Phe His Val Ala Leu Leu Gly Gly Thr Ala Glu Leu
 35 40 45
 Leu Cys Pro Leu Ser Leu Trp Pro Gly Thr Val Pro Lys Xaa Val Arg
 50 55 60
 Trp Leu Arg Ser Pro Phe Pro Gln Arg Ser Gln Ala Val His Ile Phe
 65 70 75 80
 Arg Asp Gly Lys Asp Gln Asp Glu Asp Leu Met Pro Glu Tyr Lys Gly
 85 90 95
 Arg Thr Val Leu Val Arg Asp Ala Gln Glu Gly Ser Val Thr Leu Gln
 100 105 110
 Ile Leu Asp Val Arg Leu
 115

<210> 356
 <211> 93
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (75)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 356
 Met Ser His Cys Cys Ser Leu Arg Val Asp Phe Ser Val Pro Leu Cys
 1 5 10 15
 Met Leu Leu Ser Pro Leu Leu Gly Met Ser Phe Ser Ala Cys Gln Thr
 20 25 30
 Pro Ser Lys Ser Ser Ser Asp Val Thr Phe Ser Leu Ser Thr Pro Asp
 35 40 45
 Pro Thr Pro Gln Ile Asp Leu Val Gln Pro Ser Ser Gly Phe Pro Gln
 50 55 60
 His Ser Val Gln Phe Glu Arg Ser Phe Ile Xaa Val Ile Ile Thr Phe
 65 70 75 80
 Phe Lys Asn Asn Phe Ile Phe Ile Asn Leu Ile Arg Leu
 85 90

203

<210> 357

<211> 122

<212> PRT

<213> Homo sapiens

<400> 357

```

Met Leu His Ser Leu Ala Leu Ala Glu Phe Cys Arg Asp Trp Gln His
 1           5           10           15
Cys Val Pro Ala Cys Ser Pro Thr Val Ala Val Leu Phe Pro Arg Val
          20           25           30
Gln Arg Arg Phe Phe Leu Cys Ala Leu Trp Leu Leu Arg Ala His Gly
          35           40           45
Gly Gly Leu Gly Ser Ala Ile Gln Asp Cys Leu Phe Tyr Pro Leu His
 50           55           60
Cys Leu Phe Gln Gln Tyr Glu Gly Thr Val Ile Ala His Met Ile Phe
 65           70           75           80
Gly Ser Tyr Glu Gly Ala Phe Cys Val Gly Gly Cys Gln Ile Trp Cys
          85           90           95
Ser Cys Arg Glu Asp Asn Arg Trp Arg Leu Leu Phe Gly His Ile Ala
          100          105          110
Leu Pro Pro Ile Pro Ala Cys Phe Tyr Phe
          115          120

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<210> 358

<211> 95

<212> PRT

<213> Homo sapiens

<400> 358

```

Met Gly Ala Ala Trp Pro Arg Arg Ala Arg Ser Trp Trp Ile Arg Thr
 1           5           10           15
Ser Thr Ala Ser Ser Pro Ser Pro Ser Ser Ser Ile Thr Leu Leu Trp
          20           25           30
Thr Pro Cys Met Trp Ala Glu Ser Trp Ala Cys Cys Ser Ser Pro Thr
          35           40           45
Tyr Thr Arg Thr Gly Lys Cys Ser Thr Asn Arg Thr Pro Arg Trp Pro
 50           55           60
Pro Ala Leu Thr Ser Met Pro Arg Thr Ser Thr Phe Gln Gln Trp Leu
 65           70           75           80
Ser Ser Pro Thr Phe Trp Trp Leu Ala Cys Ala Gly Asp Pro Gly
          85           90           95

```

<210> 359

<211> 129

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

204

<222> (52)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (110)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 359

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Asn | Lys | Arg | Ala | Lys | Phe | Glu | Leu | Arg | Lys | Pro | Leu | Val | Leu | Trp |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Leu | Thr | Leu | Ala | Val | Phe | Ser | Ile | Phe | Gly | Ala | Leu | Arg | Thr | Gly |
| | | | 20 | | | | | 25 | | | | | 30 | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ala | Tyr | Met | Val | Tyr | Ile | Leu | Met | Thr | Lys | Gly | Leu | Lys | Gln | Ser | Val |
| | | 35 | | | | | 40 | | | | | 45 | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Cys | Asp | Gln | Xaa | Phe | Tyr | Asn | Gly | Pro | Val | Ser | Lys | Phe | Trp | Ala | Tyr |
| | 50 | | | | | 55 | | | | | 60 | | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ala | Phe | Val | Leu | Ser | Lys | Ala | Pro | Glu | Leu | Gly | Asp | Thr | Ile | Phe | Ile |
| 65 | | | | | 70 | | | | | 75 | | | | | 80 |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ile | Leu | Arg | Lys | Gln | Lys | Leu | Ile | Phe | Leu | His | Trp | Tyr | His | His | Ile |
| | | | | 85 | | | | | 90 | | | | | 95 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Thr | Val | Leu | Leu | Tyr | Ser | Trp | Tyr | Ser | Tyr | Lys | Asp | Met | Xaa | Cys | Arg |
| | | 100 | | | | | | 105 | | | | | 110 | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Gly | Trp | Phe | Met | Thr | Met | Asn | Tyr | Gly | Val | His | Ala | Val | Met | Tyr |
| | | 115 | | | | | 120 | | | | | 125 | | | |

Ser

<210> 360

<211> 84

<212> PRT

<213> Homo sapiens

<400> 360

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Gly | Asp | Lys | Glu | Ser | Ser | Ser | Ser | Lys | Pro | Ser | Leu | Ala | Gly | Trp |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Pro | Leu | Leu | Leu | Gly | Gly | Ala | Phe | Ser | Cys | Thr | Pro | Leu | Pro | Pro |
| | | | 20 | | | | | 25 | | | | | 30 | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Arg | Gly | Glu | Ser | Gln | Gln | Pro | Asn | Gln | Thr | Ala | Gln | Val | Val | His | Leu |
| | | 35 | | | | | 40 | | | | | 45 | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Glu | Thr | Thr | Gly | Leu | Lys | His | Val | Leu | Tyr | Ser | Pro | Val | Tyr | Phe |
| | 50 | | | | | 55 | | | | | 60 | | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Cys | Cys | Tyr | Phe | Glu | Ala | Trp | Lys | Phe | Leu | Phe | Gly | Gly | Ser | Trp | Gly |
| 65 | | | | | 70 | | | | | 75 | | | | | 80 |

Tyr Ser Ser Gly

<210> 361

<211> 88

205

<212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (11)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (19)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (23)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (56)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (57)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 361
 Thr Ser Asn Val Asn Ala Gln Asn His Gln Xaa Pro Thr His Leu Arg
 1 5 10 15
 Val Asn Xaa Tyr Asp Val Xaa Phe Gly Val Asn Val Gly Asn Glu Thr
 20 25 30
 Ala Met Lys Ala Pro Glu Leu Lys Asp Val Gly Lys Trp Ala Ala Val
 35 40 45
 His Cys Pro Ala Leu Gln Gly Xaa Xaa Glu Ala Cys Leu Leu Ala Ser
 50 55 60
 Gly Gly Gly Ala Arg Leu Gln Glu Gly Pro Ala Thr Cys His Leu Pro
 65 70 75 80
 Cys Asp Gln Ala Lys Lys Trp Asn
 85

<210> 362
 <211> 116
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (11)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 362
 Met Ala Leu Asp Ile Ser Leu Phe Tyr Leu Xaa Tyr Phe Phe Phe
 1 5 10 15
 Leu Arg Trp Asn Phe Ser Leu Ile Ala Gln Ala Gly Val Gln Trp His
 20 25 30

206

Asp Leu Gly Ser Pro Gln Pro Pro Pro Pro Gly Leu Lys Arg Phe Ser
 35 40 45
 Phe Leu Gly Leu Pro Ser Ser Trp Asp Tyr Arg His Ala Pro Pro Cys
 50 55 60
 Pro Ala Asn Phe Val Phe Leu Val Glu Met Gly Phe Leu His Val Gly
 65 70 75 80
 Gln Ala Gly Leu Glu Leu Pro Thr Ser Gly Gly Pro Pro Ala Trp Ala
 85 90 95
 Ser Gln Ser Ala Gly Ile Thr Gly Val Ser His Arg Ala Trp Pro Glu
 100 105 110
 Asn Ser His Phe
 115

<210> 363
 <211> 139
 <212> PRT
 <213> Homo sapiens

<400> 363
 Met Leu Ala Met Leu Leu Cys Met Leu Val Ser Val Phe Ile Leu Gly
 1 5 10 15
 Val Pro Tyr Arg Gly Ser Leu Leu Ile Leu Phe Phe Ile Ser Ser Leu
 20 25 30
 Phe Leu Leu Ser Thr Leu Gly Met Gly Leu Leu Ile Ser Thr Ile Thr
 35 40 45
 Arg Asn Gln Phe Asn Ala Ala Gln Val Ala Leu Asn Ala Ala Phe Leu
 50 55 60
 Pro Ser Ile Met Leu Ser Gly Phe Ile Phe Gln Ile Asp Ser Met Pro
 65 70 75 80
 Ala Val Ile Arg Ala Val Thr Tyr Ile Ile Pro Ala Arg Tyr Phe Val
 85 90 95
 Ser Thr Leu Gln Ser Leu Phe Leu Ala Gly Asn Ile Pro Val Val Leu
 100 105 110
 Val Val Asn Val Leu Phe Leu Ile Ala Ser Ala Val Met Phe Ile Gly
 115 120 125
 Leu Thr Trp Leu Lys Thr Lys Arg Arg Leu Asp
 130 135

<210> 364
 <211> 82
 <212> PRT
 <213> Homo sapiens

<400> 364
 Met Gly Trp Gln Leu Arg Ala Leu Ser Ala Val Gly Leu Trp Phe Thr
 1 5 10 15
 Ala Gly Asp Ser His Leu Ser Val Gln Val Cys Gly Gly Gly Pro Ala
 20 25 30

[illegible]

```
<210> 365
<211> 59
<212> PRT
<213> Homo sapiens
```

```

<400> 365
Met Leu Cys His Ala Trp Leu Leu Leu Met Tyr Leu Phe Leu Glu Met
 1          5          10          15
Arg Ser His Cys Val Ala Gln Thr Gly Leu Glu Leu Leu Ala Ser Ser
          20          25          30
His Pro Pro Phe Ser Ala Ser Thr Val Ala Gly Ile Ser Gly Thr Cys
          35          40          45
..
His Cys Ala Leu Leu Ile Pro Phe Lys Ile Arg
 50          55

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```
<210> 366
<211> 101
<212> PRT
<213> Homo sapiens
```

```
<220>
<221> SITE
<222> (8)
<223> Xaa equals any of the naturally occurring L-amino acids
```

```

<220>
<221> SITE
<222> (100)
<223> Xaa equals any of the naturally occurring L-amino acids

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| | | | | | | | | | | | | | | | |
|-----------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| <400> 366 | | | | | | | | | | | | | | | |
| Met | Asp | His | Met | Ala | Ser | Asp | Xaa | Leu | Glu | Arg | Leu | Leu | Val | Ala | Met |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |
| Val | Phe | Pro | Cys | Ala | Gln | Glu | Val | Glu | Asn | Glu | Ile | Gly | Phe | Gly | Glu |
| | | | 20 | | | | | 25 | | | | | 30 | | |
| His | Leu | Ala | Leu | Ala | Arg | Ser | Gln | Pro | Pro | Asp | Phe | Lys | Ala | Thr | Phe |
| | | 35 | | | | | 40 | | | | | 45 | | | |
| Leu | Lys | Pro | Lys | Val | Val | Val | Gly | Gln | Val | Trp | Trp | Leu | Met | Cys | Val |
| | 50 | | | | | 55 | | | | | 60 | | | | |
| Ile | Pro | Ala | Leu | Trp | Glu | Thr | Glu | Arg | Val | Asp | His | Leu | Arg | Ser | Arg |
| 65 | | | | | 70 | | | | | 75 | | | | | 80 |

208

Ala Gln Asp Gln Pro Ala Gln Cys Gly Lys Thr Pro Ser Leu Leu Lys
 85 90 95

Ile Gln Thr Xaa Asn
 100

<210> 367
 <211> 31
 <212> PRT
 <213> Homo sapiens

<400> 367
 Met Ile His Leu Phe Leu Leu Pro Cys Pro Asn Cys Val Phe Leu Leu
 1 5 10 15
 Leu His Leu Phe Phe Gln Gln Cys Ala Ala Ser Trp Thr Thr Ser
 20 25 30

<210> 368
 <211> 118
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (34)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 368
 Ala Asn Thr Ser Thr Arg Ala Ala Leu Tyr Cys Leu Phe Leu Ser Phe
 1 5 10 15
 Ile Met Phe Ala Ser Val Leu Gln Ile Asn Pro Arg Ser Trp Leu Met
 20 25 30
 Lys Xaa Val Ile Thr Val Leu Ala Ala Cys Leu Glu Ser Glu Asn Gln
 35 40 45
 Asn Ala Gln Arg Ile Gly Ala Ala Ala Leu Trp Ala Leu Ile Tyr Asn
 50 55 60
 Tyr Gln Lys Ala Lys Thr Ala Leu Lys Ser Pro Ser Val Lys Arg Arg
 65 70 75 80
 Val Asp Glu Ala Tyr Ser Leu Ala Lys Lys Thr Phe Pro Asn Ser Glu
 85 90 95
 Ala Asn Pro Leu Asn Ala Tyr Tyr Leu Lys Cys Leu Glu Asn Leu Val
 100 105 110
 Gln Leu Leu Asn Ser Ser
 115

<210> 369
 <211> 87
 <212> PRT
 <213> Homo sapiens

<400> 369
 Met Thr Leu Leu Leu Thr Leu Glu Val Asp Pro Gly Thr Gln Gln Arg

209

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| 1 | | 5 | | 10 | | 15 | | | | | | | | | |
| Ala | Gly | Val | Gly | Ser | Gln | Gly | Gln | Ala | Val | Leu | Pro | Gly | Leu | Thr | Cys |
| | | 20 | | | | | | 25 | | | | | 30 | | |
| Phe | Leu | Leu | Thr | Phe | Leu | Leu | Ala | Ala | Ser | Val | Tyr | Ile | Thr | Gln | Ser |
| | | 35 | | | | | 40 | | | | | 45 | | | |
| Ala | Trp | Asp | Asn | Val | Glu | Val | Ala | Glu | Val | Thr | Gly | Tyr | Phe | Met | Phe |
| | 50 | | | | | 55 | | | | | 60 | | | | |
| Leu | His | Gly | Ile | Phe | Leu | Phe | Leu | Ile | Gly | Arg | Arg | Arg | Gln | Lys | Leu |
| 65 | | | | | 70 | | | | | 75 | | | | | 80 |
| Glu | Glu | Met | Gly | Leu | Leu | Ser | | | | | | | | | |
| | | | | 85 | | | | | | | | | | | |

<210> 370
 <211> 73
 <212> PRT
 <213> Homo sapiens

| |
|---|
| <400> 370 |
| Met Tyr Pro Val Tyr Thr Thr Ser Asp Phe Cys Ser Gly Thr Phe Val |
| 1 5 10 15 |
| Leu Ile Phe Ala Trp Leu Thr Leu Ser Glu Leu Val Arg Val Leu His |
| 20 25 30 |
| Arg Lys Ile Ile Asn Trp Phe Phe Ile Phe Leu Arg Arg Phe Tyr Tyr |
| 35 40 45 |
| Gly Glu Leu Ala Tyr Ala Asn Met Glu Thr Thr Met Cys His Leu Gln |
| 50 55 60 |
| Ala Gly Asp Pro Arg Gln Leu Val Val |
| 65 70 |

<210> 371
 <211> 81
 <212> PRT
 <213> Homo sapiens

| |
|---|
| <400> 371 |
| Met Tyr Ser Pro Ser Leu Tyr Leu Leu Pro Ser Leu Pro Ser Leu Leu |
| 1 5 10 15 |
| Gln Leu Ser Leu Ser Arg Ser Pro Arg Phe Asn Lys Gly Leu Gln Arg |
| 20 25 30 |
| Ala Met Glu Lys Thr Met Lys Gly Ser Thr Ile Lys Ile Leu Leu Tyr |
| 35 40 45 |
| Phe Phe His His Ile Tyr Ala Ser Leu His Thr Phe Ile Pro Leu Pro |
| 50 55 60 |
| Asn Pro Ser Ile Phe Leu Cys Ile Ser Lys Tyr Ile Ala Asp Ile Ser |
| 65 70 75 80 |

Thr

210

<210> 372
 <211> 61
 <212> PRT
 <213> Homo sapiens

 <220>
 <221> SITE
 <222> (6)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <220>
 <221> SITE
 <222> (43)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <400> 372
 Met Ser Lys Lys Ser Xaa Ser Tyr Lys Ile Arg Tyr Phe Ser Gln Ala
 1 5 10 15
 Trp Gln Leu Met Pro Val Ile Leu Val Leu Trp Glu Ala Glu Ala Gly
 20 25 30
 Gly Ser Leu Glu Ala Arg Gln Asp His Ile Xaa Arg Leu Cys Leu Cys
 35 40 45
 Lys Lys Lys Lys Arg Ala Ala Pro Leu Phe Phe Phe Phe
 50 55 60

 <210> 373
 <211> 83
 <212> PRT
 <213> Homo sapiens

 <400> 373
 Met Leu Cys Ser Ser Phe Leu Pro Leu Ser Thr Ala Ala Ile Trp Ala
 1 5 10 15
 Ala Leu Phe Ser Gly Met Gly Ala Val Arg His Ser Pro Ser Glu Gly
 20 25 30
 Lys Arg Ser Leu Lys Ser Ser Arg Cys Leu His Phe Trp Pro Leu Pro
 35 40 45
 Thr Gly Cys Ser Ser Pro Pro Pro Pro Cys Asn Val Thr Thr Lys Asn
 50 55 60
 Val Ser Arg Cys Cys Gln Lys Ser Ser Arg Asp Gly Arg Val Arg Leu
 65 70 75 80
 Pro Pro Arg

 <210> 374
 <211> 84
 <212> PRT
 <213> Homo sapiens

 <400> 374
 Met Gly Leu Arg Leu Pro Pro Pro Leu Cys Trp Phe Leu Cys Leu Thr
 1 5 10 15

211

Ser Thr Gly Gln Val Pro Met Ala Gln Ala Arg Ala Gly Val Gln Gly
 20 25 30
 Pro Met Asp Gly Arg Met Pro Ser Asn Gly Cys Leu Pro Val Ser Pro
 35 40 45
 Arg Thr Pro Tyr Gly Met Pro Tyr Leu Gly Ala Leu Trp Pro Cys Trp
 50 55 60
 Pro Cys Ser Trp Gln Gly Arg Ser Thr Ser Arg His Pro Cys Gln Gln
 65 70 75 80
 Asp Leu Ser Gly

<210> 375
 <211> 143
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (97)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (99)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (104)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (107)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 375
 Met Asp Val Gly Pro Ser Ser Leu Pro His Leu Gly Leu Lys Leu Leu
 1 5 10 15
 Leu Leu Leu Leu Leu Leu Pro Leu Arg Gly Gln Ala Asn Thr Gly Cys
 20 25 30
 Tyr Gly Ile Pro Gly Met Pro Gly Leu Pro Gly Ala Pro Gly Lys Asp
 35 40 45
 Gly Tyr Asp Gly Leu Pro Gly Pro Lys Gly Glu Pro Gly Ile Pro Ala
 50 55 60
 Ile Pro Gly Ile Arg Gly Pro Lys Gly Gln Lys Gly Glu Pro Gly Leu
 65 70 75 80
 Pro Gly His Pro Gly Lys Asn Gly Pro Met Gly Pro Pro Gly Met Pro
 85 90 95
 Xaa Val Xaa Gly Pro Met Gly Xaa Pro Gly Xaa Pro Glu Ile Pro Val
 100 105 110
 Ser Val His Gly His Ser Ala Asp Pro Pro Ala Pro Cys Thr Gln Gln

212

| | | |
|-----------------------------|---------------------------------|-----|
| 115 | 120 | 125 |
| Pro Asp Gln Ile Gln Arg Gly | Pro His Gln Pro Ala Gly Arg Leu | |
| 130 | 135 | 140 |

<210> 376
 <211> 245
 <212> PRT
 <213> Homo sapiens

<400> 376
 Met Asp Val Gly Pro Ser Ser Leu Pro His Leu Gly Leu Lys Leu Leu
 1 5 10 15
 Leu Leu Leu Leu Leu Leu Pro Leu Arg Gly Gln Ala Asn Thr Gly Cys
 20 25 30
 Tyr Gly Ile Pro Gly Met Pro Gly Leu Pro Gly Ala Pro Gly Lys Asp
 35 40 45
 Gly Tyr Asp Gly Leu Pro Gly Pro Lys Gly Glu Pro Gly Ile Pro Ala
 50 55 60
 Ile Pro Gly Ile Arg Gly Pro Lys Gly Gln Lys Gly Glu Pro Gly Leu
 65 70 75 80
 Pro Gly His Pro Gly Lys Asn Gly Pro Met Gly Pro Pro Gly Met Pro
 85 90 95
 Gly Val Pro Gly Pro Met Gly Ile Pro Gly Glu Pro Gly Glu Glu Gly
 100 105 110
 Arg Tyr Lys Gln Lys Phe Gln Ser Val Phe Thr Val Thr Arg Gln Thr
 115 120 125
 His Gln Pro Pro Ala Pro Asn Ser Leu Ile Arg Phe Asn Ala Val Leu
 130 135 140
 Thr Asn Pro Gln Gly Asp Tyr Asp Thr Ser Thr Gly Lys Phe Thr Cys
 145 150 155 160
 Lys Val Pro Gly Leu Tyr Tyr Phe Val Tyr His Ala Ser His Thr Ala
 165 170 175
 Asn Leu Cys Val Leu Leu Tyr Arg Ser Gly Val Lys Val Val Thr Phe
 180 185 190
 Cys Gly His Thr Ser Lys Thr Asn Gln Val Asn Ser Gly Gly Val Leu
 195 200 205
 Leu Arg Leu Gln Val Gly Glu Glu Val Trp Leu Ala Val Asn Asp Tyr
 210 215 220
 Tyr Asp Met Val Gly Ile Gln Gly Ser Asp Ser Val Phe Ser Gly Phe
 225 230 235 240
 Leu Leu Phe Pro Asp
 245

<210> 377
 <211> 83
 <212> PRT

213

<213> Homo sapiens

<400> 377

```

Met Cys Ala Met Ala Pro Leu Trp Ser Pro Leu Cys Pro Ser Ile Cys
 1           5           10           15
Met Cys Ser Val Ser Leu Ala Cys Val Arg Val Arg Val Ser Ala Tyr
           20           25           30
Ala Ser Thr His Trp Ala Leu Gly Cys Ser Gln Gly Lys Phe Asp Leu
           35           40           45
Glu Arg Leu Ser Ser Pro Trp Asn Gln Asp Phe Leu Ser Pro Pro His
           50           55           60
Pro Gly Pro Val Pro Pro Trp Leu Ser Gly Tyr Trp Gly Met Glu Thr
           65           70           75           80
Leu Gly Glu

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<210> 378

<211> 91

<212> PRT

<213> Homo sapiens

<400> 378

```

Met Arg Pro Gln Glu Leu Pro Arg Leu Ala Phe Pro Leu Leu Leu Leu
 1           5           10           15
Leu Leu Leu Leu Leu Pro Pro Pro Pro Cys Pro Ala His Ser Ala Thr
           20           25           30
Arg Phe Asp Pro Thr Trp Glu Ser Leu Asp Ala Arg Gln Leu Pro Ala
           35           40           45
Trp Phe Asp Gln Ala Lys Phe Gly Ile Phe Ile His Trp Gly Val Phe
           50           55           60
Ser Val Pro Ser Phe Gly Ser Glu Trp Phe Trp Leu Tyr Leu Val Gly
           65           70           75           80
Val Arg Ile Phe Val Glu Leu Glu Cys His Arg
           85           90

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<210> 379

<211> 336

<212> PRT

<213> Homo sapiens

<400> 379

```

Met Leu Glu Thr Gly Leu Phe Phe Leu Leu Ser Trp Ser Ala Phe Leu
 1           5           10           15
Ser Ala Glu Ala Ala Gly Leu Thr Gly Ile Val Ala Val Leu Phe Cys
           20           25           30
Gly Val Thr Gln Ala His Tyr Thr Tyr Asn Asn Leu Ser Ser Asp Ser
           35           40           45
Lys Ile Arg Thr Lys Gln Leu Phe Glu Phe Met Asn Phe Leu Ala Glu
           50           55           60

```

214

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asn | Val | Ile | Phe | Cys | Tyr | Met | Gly | Leu | Ala | Leu | Phe | Thr | Phe | Gln | Asn |
| 65 | | | | | 70 | | | | | 75 | | | | | 80 |
| His | Ile | Phe | Asn | Ala | Leu | Phe | Ile | Leu | Gly | Ala | Phe | Leu | Ala | Ile | Phe |
| | | | | 85 | | | | | 90 | | | | | 95 | |
| Val | Ala | Arg | Ala | Cys | Asn | Ile | Tyr | Pro | Leu | Ser | Phe | Leu | Leu | Asn | Leu |
| | | | 100 | | | | | 105 | | | | | 110 | | |
| Gly | Arg | Lys | Gln | Lys | Ile | Pro | Trp | Asn | Phe | Gln | His | Met | Met | Met | Phe |
| | | 115 | | | | | 120 | | | | | 125 | | | |
| Ser | Gly | Leu | Arg | Gly | Ala | Ile | Ala | Phe | Ala | Leu | Ala | Ile | Arg | Asn | Thr |
| | 130 | | | | | 135 | | | | | 140 | | | | |
| Glu | Ser | Gln | Pro | Lys | Gln | Met | Met | Phe | Thr | Thr | Thr | Leu | Leu | Leu | Val |
| 145 | | | | | 150 | | | | | 155 | | | | | 160 |
| Phe | Phe | Thr | Val | Trp | Val | Phe | Gly | Gly | Gly | Thr | Thr | Pro | Met | Leu | Thr |
| | | | | 165 | | | | | 170 | | | | | 175 | |
| Trp | Leu | Gln | Ile | Arg | Val | Gly | Val | Asp | Leu | Asp | Glu | Asn | Leu | Lys | Glu |
| | | | 180 | | | | | 185 | | | | | 190 | | |
| Asp | Pro | Ser | Ser | Gln | His | Gln | Glu | Ala | Asn | Asn | Leu | Asp | Lys | Asn | Met |
| | | 195 | | | | | 200 | | | | | 205 | | | |
| Thr | Lys | Ala | Glu | Ser | Ala | Arg | Leu | Phe | Arg | Met | Trp | Tyr | Ser | Phe | Asp |
| | 210 | | | | | 215 | | | | | 220 | | | | |
| His | Lys | Tyr | Leu | Lys | Pro | Ile | Leu | Thr | His | Ser | Gly | Pro | Pro | Leu | Thr |
| 225 | | | | | 230 | | | | | 235 | | | | | 240 |
| Thr | Thr | Leu | Pro | Glu | Trp | Cys | Gly | Pro | Ile | Ser | Arg | Leu | Leu | Thr | Ser |
| | | | | 245 | | | | | 250 | | | | | 255 | |
| Pro | Gln | Ala | Tyr | Gly | Glu | Gln | Leu | Lys | Glu | Asp | Asp | Val | Glu | Cys | Ile |
| | | | 260 | | | | | 265 | | | | | 270 | | |
| Val | Asn | Gln | Asp | Glu | Leu | Ala | Ile | Asn | Tyr | Gln | Glu | Gln | Ala | Ser | Ser |
| | | 275 | | | | | 280 | | | | | 285 | | | |
| Pro | Cys | Ser | Pro | Pro | Ala | Arg | Leu | Gly | Leu | Asp | Gln | Lys | Ala | Ser | Pro |
| | 290 | | | | | 295 | | | | | 300 | | | | |
| Gln | Thr | Pro | Gly | Lys | Glu | Asn | Ile | Tyr | Glu | Gly | Asp | Leu | Gly | Leu | Gly |
| 305 | | | | | 310 | | | | | 315 | | | | | 320 |
| Gly | Tyr | Glu | Leu | Lys | Leu | Glu | Gln | Thr | Leu | Gly | Gln | Ser | Gln | Leu | Asn |
| | | | | 325 | | | | | 330 | | | | | 335 | |

<210> 380

<211> 72

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (5)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (19)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (23)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (25)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (27)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (32)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (33)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (35)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (40)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (42)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (47)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (50)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (51)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (55)
<223> Xaa equals any of the naturally occurring L-amino acids

216

<220>

<221> SITE

<222> (68)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 380

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Gln | Trp | Leu | Xaa | Ile | Thr | Pro | Arg | Leu | Phe | Tyr | Phe | Pro | Leu | Leu |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Leu | Xaa | Leu | Gly | Ser | Xaa | Lys | Xaa | Leu | Xaa | Ile | Ser | Ile | Leu | Xaa |
| | | | 20 | | | | | 25 | | | | | 30 | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Xaa | Gly | Xaa | Val | Leu | Leu | His | Xaa | Ser | Xaa | Arg | Met | His | Gly | Xaa | Asn |
| | | 35 | | | | | 40 | | | | | 45 | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Xaa | Xaa | Gln | Ser | Leu | Xaa | Phe | Lys | Val | Lys | Leu | Ser | Ser | Pro | Leu |
| | 50 | | | | | 55 | | | | | 60 | | | | |

| | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|
| Pro | Ser | Gln | Xaa | Leu | Gly | Leu | Arg |
| 65 | | | | | 70 | | |

<210> 381

<211> 75

<212> PRT

<213> Homo sapiens

<400> 381

| | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Gly | Ala | Ser | Leu | Cys | Leu | Thr | Gln | Leu | Leu | Leu | Leu | Gly | Lys |
| 1 | | | | 5 | | | | | 10 | | | | 15 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Gly | Leu | Gly | Gln | Ala | Ser | Ile | Pro | Leu | Val | Lys | Thr | Pro | Ala | Gly |
| | | | 20 | | | | | 25 | | | | | 30 | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| His | Gln | Ala | Phe | Trp | Thr | Arg | Thr | His | Thr | His | Thr | His | Thr | His | Thr |
| | | 35 | | | | | 40 | | | | | 45 | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| His | Lys | Thr | Ser | Gln | Gln | Ala | Ser | Cys | Ser | Asp | Leu | Ser | Ser | Arg | Val |
| | 50 | | | | | 55 | | | | | 60 | | | | |

| | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Thr | Ser | Ala | Ala | Pro | Pro | Ser | His | Pro | Phe | Leu |
| 65 | | | | | 70 | | | | | 75 |

<210> 382

<211> 81

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (77)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 382

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Cys | Val | His | Thr | Cys | Val | Cys | Met | Cys | Val | His | Thr | Cys | Val | Cys |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | His | Ala | Cys | Val | Trp | Ala | His | Val | Cys | Met | Cys | Val | Cys | Glu | Cys |
| | | | 20 | | | | | 25 | | | | | 30 | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Cys | Trp | Gly | Gly | Gly | Met | Ala | Leu | Gly | Lys | Val | Cys | Pro | Gly | Trp |
| | | | 35 | | | | 40 | | | | | | 45 | | |

217

[illegible]

```
<210> 383
<211> 117
<212> PRT
<213> Homo sapiens
```

```
<220>
<221> SITE
<222> (116)
<223> Xaa equals any of the naturally occurring L-amino acids
```

```

<400> 383
Met His Pro Pro Pro Gly Val Trp Leu Leu His Leu His Thr Pro Leu
  1          5          10          15

Arg Gly Phe Cys Leu Pro Leu Pro Leu Arg Ser Gln Glu Ala Val Pro
      20          25          30

Gly Arg Gly Arg Arg His Leu Ser Pro Gln Leu Leu Thr Pro His Pro
  35          40          45

Leu Thr Ser Ser Pro Phe Val Lys Tyr Thr Gln Asp Glu Thr Cys Thr
  50          55          60

Gln Trp Leu Thr Ala Ala Arg Phe Val Thr Ala Arg Gly Gly Glu His
  65          70          75          80

Arg Thr Pro Ser Glu Gly Glu Gly Ile Ser Thr Ala Pro Pro Cys
      85          90          95

Trp Asn Glu Thr Gln Pro Gln Gly Gly Ala Thr Ser Asp Pro Gly His
      100          105          110

Ser Ala Asp Xaa Pro
      115

```

```
<210> 384
<211> 167
<212> PRT
<213> Homo sapiens
```

<400> 384
Pro Gly Pro Gly Ser Cys Leu Leu His Leu Ser Ser Gln Asn Leu Trp
1 5 10 15
Gln Pro Glu Phe Phe Asn Ser Leu Ser Leu Ser Leu His Gln Leu His
20 25 30
Ser Arg Ile Asn Arg Lys Val Ala Ala Arg Pro Ala Gly Pro Leu Val
35 40 45
Ser Leu Pro Leu His Leu Gly Val Ser Gln Pro Leu Pro Gly Ser Pro
50 55 60

218

Gln Glu Ala Met Ala Pro Leu Ala Phe Val Cys Leu Ser Gly Gly Ala
 65 70 75 80
 Asp Ser Arg Gly Thr Cys Pro Ser Ala Ala Glu Trp Pro Pro Cys Pro
 85 90 95
 Ala Lys Pro Asp Val His Ser Pro Gly Ala Pro Pro Pro Pro Leu Ser
 100 105 110
 Cys Pro Gly Pro Trp Gly Thr Asn Ser Pro Ile Ser Thr Arg Ala Leu
 115 120 125
 Ala His His His Gly Thr Leu Pro Pro Arg Pro Ser Pro Pro Leu Leu
 130 135 140
 Cys Pro Ser Trp Pro His Leu Ala Ser Pro Gly Gly Glu Leu Ser Pro
 145 150 155 160
 Ala Val Pro Thr Leu Pro Pro
 165

<210> 385

<211> 277

<212> PRT

<213> Homo sapiens

<400> 385

Arg Arg Val Val Ile Asp Pro Gln Glu Lys Pro Ser Glu Glu Pro Leu
 1 5 10 15
 Gly Asp Arg Arg Thr Val Ile Asp Lys Cys Ser Pro Pro Leu Glu Phe
 20 25 30
 Leu Asp Asp Ser Asp Ser His Leu Glu Ile Gln Lys His Lys Asp Arg
 35 40 45
 Glu Val Val Met Glu His Pro Ser Ser Gly Ser Asp Trp Ser Asp Val
 50 55 60
 Glu Glu Ile Ser Thr Val Arg Phe Ser Gln Glu Glu Pro Val Ser Leu
 65 70 75 80
 Lys Pro Ser Ala Val Pro Glu Pro Ser Ser Phe Thr Thr Asp Tyr Val
 85 90 95
 Met Tyr Pro Pro His Leu Tyr Ser Ser Pro Trp Cys Asp Tyr Ala Ser
 100 105 110
 Tyr Trp Thr Ser Ser Pro Lys Pro Ser Ser Tyr Pro Ser Thr Gly Ser
 115 120 125
 Ser Ser Asn Asp Ala Ala Gln Val Gly Lys Ser Ser Arg Ser Arg Met
 130 135 140
 Ser Asp Tyr Ser Pro Asn Ser Thr Gly Ser Val Gln Asn Thr Ser Arg
 145 150 155 160
 Asp Met Glu Ala Ser Glu Glu Gly Trp Ser Gln Asn Ser Arg Ser Phe
 165 170 175
 Arg Phe Ser Arg Ser Ser Glu Glu Arg Glu Val Lys Glu Lys Arg Thr
 180 185 190
 Phe Gln Glu Glu Met Pro Pro Arg Pro Cys Gly Gly His Ala Ser Ser

219

| 195 | | | | | 200 | | | | | 205 | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Leu | Pro | Lys | Ser | His | Leu | Glu | Pro | Ser | Leu | Glu | Glu | Gly | Phe | Ile |
| | 210 | | | | | 215 | | | | | 220 | | | | |
| Asp | Thr | His | Cys | His | Leu | Asp | Met | Leu | Tyr | Ser | Lys | Leu | Ser | Phe | Gln |
| 225 | | | | | 230 | | | | | 235 | | | | | 240 |
| Gly | Thr | Phe | Thr | Lys | Phe | Arg | Lys | Ile | Tyr | Ser | Ser | Ser | Phe | Pro | Lys |
| | | | | 245 | | | | | 250 | | | | | 255 | |
| Glu | Phe | Gln | Gly | Cys | Ile | Ser | Asp | Phe | Cys | Val | Arg | Gly | Gly | Lys | Ala |
| | | | 260 | | | | | 265 | | | | | 270 | | |
| Glu | Met | Thr | Trp | Lys | | | | | | | | | | | |
| | | | 275 | | | | | | | | | | | | |

<210> 386

<211> 172

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (153)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 386

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Trp | Phe | Ala | Ala | Leu | Val | Lys | Cys | Leu | Pro | Val | Leu | Cys | Leu | Ala | Gly |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Phe | Leu | Trp | Val | Met | Ser | Pro | Ser | Gly | Gly | Tyr | Thr | Gln | Leu | Leu | Gln |
| | | | 20 | | | | | 25 | | | | | 30 | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Ala | Leu | Val | Cys | Ser | Ala | Val | Gly | Asp | Ala | Cys | Leu | Ile | Trp | Pro |
| | | 35 | | | | | 40 | | | | | 45 | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ala | Ala | Phe | Val | Pro | Gly | Met | Ala | Ala | Phe | Ala | Thr | Ala | His | Leu | Leu |
| | 50 | | | | | 55 | | | | | 60 | | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Tyr | Val | Trp | Ala | Phe | Gly | Phe | Ser | Pro | Leu | Gln | Pro | Gly | Leu | Leu | Leu |
| 65 | | | | | 70 | | | | | 75 | | | | | 80 |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Ile | Ile | Leu | Ala | Pro | Gly | Pro | Tyr | Leu | Ser | Leu | Val | Leu | Gln | His |
| | | | | 85 | | | | | 90 | | | | | 95 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Glu | Pro | Asp | Met | Val | Leu | Pro | Val | Ala | Ala | Tyr | Gly | Leu | Ile | Leu |
| | | | 100 | | | | | 105 | | | | | 110 | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Ala | Met | Leu | Trp | Arg | Gly | Leu | Ala | Gln | Gly | Gly | Ser | Ala | Gly | Trp |
| | | 115 | | | | | 120 | | | | | 125 | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Ala | Leu | Leu | Phe | Thr | Leu | Ser | Asp | Gly | Val | Leu | Ala | Trp | Asp | Thr |
| | 130 | | | | | 135 | | | | | 140 | | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Phe | Ala | Gln | Pro | Leu | Pro | His | Ala | Xaa | Leu | Val | Ile | Met | Thr | Thr | Tyr |
| 145 | | | | | 150 | | | | | 155 | | | | | 160 |

| | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Tyr | Ala | Ala | Gln | Leu | Leu | Ile | Thr | Leu | Ser | Ala | Leu |
| | | | | 165 | | | | | 170 | | |

<210> 387

<211> 156

<212> PRT

<213> Homo sapiens

220

<400> 387

```

Arg Pro Gly Ala Asp Cys Glu Val Cys Lys Glu Phe Leu Asn Arg Phe
 1           5           10           15
Tyr Lys Ser Leu Ile Asp Arg Gly Val Asn Phe Ser Leu Asp Thr Ile
          20           25           30
Glu Lys Glu Leu Ile Ser Phe Cys Leu Asp Thr Lys Gly Lys Glu Asn
          35           40           45
Arg Leu Cys Tyr Tyr Leu Gly Ala Thr Lys Asp Ala Ala Thr Lys Ile
          50           55           60
Leu Ser Glu Val Thr Arg Pro Met Ser Val His Met Pro Ala Met Lys
          65           70           75           80
Ile Cys Glu Lys Leu Lys Lys Leu Asp Ser Gln Ile Cys Glu Leu Lys
          85           90           95
Tyr Glu Lys Thr Leu Asp Leu Ala Ser Val Asp Leu Arg Lys Met Arg
          100          105          110
Val Ala Glu Leu Lys Gln Ile Leu His Ser Trp Gly Glu Glu Cys Arg
          115          120          125
Ala Cys Ala Glu Lys Thr Asp Tyr Val Asn Leu Ile Gln Glu Leu Ala
          130          135          140
Pro Lys Tyr Ala Ala Thr His Pro Lys Thr Glu Leu
          145          150          155

```

<210> 388

<211> 268

<212> PRT

<213> Homo sapiens

<400> 388

```

Phe Phe Ser Val Tyr Ala Gln Leu Trp Leu Val Leu Leu Tyr Gly His
 1           5           10           15
Lys Arg Leu Ser Tyr Gln Thr Val Phe Leu Ala Leu Cys Leu Leu Trp
          20           25           30
Ala Ala Leu Arg Thr Thr Leu Phe Ser Phe Tyr Phe Arg Asp Thr Pro
          35           40           45
Arg Ala Asn Arg Leu Gly Pro Leu Pro Phe Trp Leu Leu Tyr Cys Cys
          50           55           60
Pro Val Cys Leu Gln Phe Phe Thr Leu Thr Leu Met Asn Leu Tyr Phe
          65           70           75           80
Ala Gln Val Val Phe Lys Ala Lys Val Lys Arg Arg Pro Glu Met Ser
          85           90           95
Arg Gly Leu Leu Ala Val Arg Gly Ala Phe Val Gly Ala Ser Leu Leu
          100          105          110
Phe Leu Leu Val Asn Val Leu Cys Ala Val Leu Ser His Arg Arg Arg
          115          120          125
Ala Gln Pro Trp Ala Leu Leu Leu Val Arg Val Leu Val Ser Asp Ser
          130          135          140
Leu Phe Val Ile Cys Ala Leu Ser Leu Ala Ala Cys Leu Cys Leu Val
          145          150          155          160

```

221

Ala Arg Arg Ala Pro Ser Thr Ser Ile Tyr Leu Glu Ala Lys Gly Thr
 165 170 175
 Ser Val Cys Gln Ala Ala Ala Met Gly Gly Ala Met Val Leu Leu Tyr
 180 185 190
 Ala Ser Arg Ala Cys Tyr Asn Leu Thr Ala Leu Ala Leu Ala Pro Gln
 195 200 205
 Ser Arg Leu Asp Thr Phe Asp Tyr Asp Trp Tyr Asn Val Ser Asp Gln
 210 215 220
 Ala Asp Leu Val Asn Asp Leu Gly Asn Lys Gly Tyr Leu Val Phe Gly
 225 230 235 240
 Leu Ile Leu Phe Val Trp Glu Leu Leu Pro Thr Thr Leu Leu Val Gly
 245 250 255
 Phe Phe Arg Val His Arg Pro Pro Gln Asp Leu Ser
 260 265
 <210> 389
 <211> 222
 <212> PRT
 <213> Homo sapiens
 <400> 389
 Ser Glu Lys Arg Tyr Pro Gln Pro Arg Gly Gln Lys Lys Lys Lys Val
 1 5 10 15
 Val Lys Tyr Gly Met Gly Gly Met Ile Ile Val Leu Leu Ile Cys Ile
 20 25 30
 Val Trp Phe Pro Leu Leu Phe Met Ser Leu Ile Lys Ser Val Ala Gly
 35 40 45
 Val Ile Asn Gln Pro Leu Asp Val Ser Val Thr Ile Thr Leu Gly Gly
 50 55 60
 Tyr Gln Pro Ile Phe Thr Met Ser Ala Gln Gln Ser Gln Leu Lys Ile
 65 70 75 80
 Met Asp Gln Gln Ser Phe Asn Lys Phe Ile Gln Ala Phe Ser Arg Asp
 85 90 95
 Thr Gly Ala Met Gln Phe Leu Glu Asn Tyr Glu Lys Glu Asp Ile Thr
 100 105 110
 Val Ala Glu Leu Glu Gly Asn Ser Asn Ser Leu Trp Thr Ile Ser Pro
 115 120 125
 Pro Ser Lys Gln Lys Met Ile His Glu Leu Leu Asp Pro Asn Ser Ser
 130 135 140
 Phe Ser Val Val Phe Ser Trp Ser Ile Gln Arg Asn Leu Ser Leu Gly
 145 150 155 160
 Ala Lys Ser Glu Ile Ala Thr Asp Lys Leu Ser Phe Pro Leu Lys Asn
 165 170 175
 Ile Thr Arg Lys Asn Ile Ala Lys Met Ile Ala Gly Asn Ser Thr Glu
 180 185 190
 Ser Ser Lys Thr Pro Val Thr Ile Glu Lys Ile Tyr Pro Tyr Tyr Val
 195 200 205

222

Lys Ala Pro Ser Asp Ser Asn Ser Lys Pro Ile Lys Gln Leu
 210 215 220
 <210> 390
 <211> 267
 <212> PRT
 <213> Homo sapiens
 <400> 390
 Thr Asp Gly Glu Ser Arg Phe Tyr Ser Leu Gly His Leu Ser Ile Gln
 1 5 10 15
 Arg Ala Ala Leu Val Val Leu Glu Asn Tyr Tyr Lys Asp Phe Thr Ile
 20 25 30
 Tyr Asn Pro Asn Leu Leu Thr Ala Ser Lys Phe Arg Ala Ala Lys His
 35 40 45
 Met Ala Gly Leu Lys Val Tyr Asn Val Asp Gly Pro Ser Asn Asn Ala
 50 55 60
 Thr Gly Gln Ser Arg Ala Met Ile Ala Ala Ala Arg Arg Arg Asp
 65 70 75 80
 Ser Ser His Asn Glu Leu Tyr Tyr Glu Glu Ala Glu His Glu Arg Arg
 85 90 95
 Val Lys Lys Arg Lys Ala Arg Leu Val Val Ala Val Glu Glu Ala Phe
 100 105 110
 Ile His Ile Gln Arg Leu Gln Ala Glu Glu Gln Gln Lys Ala Pro Gly
 115 120 125
 Glu Val Met Asp Pro Arg Glu Ala Ala Gln Ala Ile Phe Pro Ser Met
 130 135 140
 Ala Arg Ala Leu Gln Lys Tyr Leu Arg Ile Thr Arg Gln Gln Asn Tyr
 145 150 155 160
 His Ser Met Glu Ser Ile Leu Gln His Leu Ala Phe Cys Ile Thr Asn
 165 170 175
 Gly Met Thr Pro Lys Ala Phe Leu Glu Arg Tyr Leu Ser Ala Gly Pro
 180 185 190
 Thr Leu Gln Tyr Asp Lys Asp Arg Trp Leu Ser Thr Gln Trp Arg Leu
 195 200 205
 Val Ser Asp Glu Ala Leu Thr Asn Gly Leu Arg Asp Gly Ile Val Phe
 210 215 220
 Val Leu Lys Cys Leu Asp Phe Ser Leu Val Val Asn Val Lys Lys Ile
 225 230 235 240
 Pro Phe Ile Ile Leu Ser Glu Glu Phe Ile Asp Pro Lys Ser His Lys
 245 250 255
 Phe Val Leu Arg Leu Gln Ser Glu Thr Ser Val
 260 265

<210> 391
 <211> 97
 <212> PRT
 <213> Homo sapiens

223

<400> 391

Gln Ser Cys Tyr Val Ala Gln Ala Gly Val Gln Trp His Asn His Ser
 1 5 10 15

Ser Leu Gln Pro Leu Ser Pro Gly Phe Lys Arg Phe Phe Cys Leu Asn
 20 25 30

Leu Pro Ser Ser Trp Asp Tyr Arg His Met Ala Thr Cys Pro Trp Leu
 35 40 45

Ile Phe Val Phe Leu Val Glu Met Glu Phe Arg His Val Gly Gln Ala
 50 55 60

Gly Leu Gly Leu Leu Thr Ser Ser Asp Leu Pro Ala Leu Ala Phe Gln
 65 70 75 80

Ser Ala Gly Ile Thr Gly Leu Ser His His Ala Trp Pro Gly Arg Phe
 85 90 95

Leu

<210> 392

<211> 44

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (16)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (28)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (43)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 392

Phe Phe Val Phe Leu Val Glu Met Gly Phe Arg His Val Gly Gln Xaa
 1 5 10 15

Gly Leu Glu Leu Leu Thr Ser Gly Tyr Pro Ser Xaa Leu Thr Ser Gln
 20 25 30

Ser Ala Gly Ile Thr Gly Met Ser His His Xaa Arg
 35 40

<210> 393

<211> 25

<212> PRT

<213> Homo sapiens

<400> 393

Gln Gly Ser Cys Leu Ser Leu Pro Ser Ser Trp Gly Tyr Arg Cys Pro
 1 5 10 15

Pro Pro His Pro Gly Asn Phe Leu Tyr
 20 25

<210> 394

<211> 25

224

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (6)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 394

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Phe | Phe | Cys | Phe | Xaa | Arg | Trp | Glu | Pro | Cys | Ser | Val | Thr | Gln | Ala |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |

| | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Val | Gln | Trp | Cys | Asp | Leu | Ser | Ser |
| | | 20 | | | | | | 25 |

<210> 395

<211> 18

<212> PRT

<213> Homo sapiens

<400> 395

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Pro | Ala | Ser | Ala | Ser | Arg | Val | Ala | Gly | Val | Thr | Gly | Ala | Pro | His | His |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |

Thr Gln

<210> 396

<211> 15

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (2)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 396

| | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Xaa | Lys | Cys | Trp | Asp | Tyr | Arg | Tyr | Glu | Pro | Pro | Arg | Pro | Ala |
| 1 | | | | 5 | | | | | 10 | | | | | 15 |

<210> 397

<211> 157

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (141)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 397

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Asn | Pro | Glu | Val | Trp | Met | Asn | Thr | Ser | Glu | Ile | Ile | Ile | Tyr | Asn |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Tyr | Pro | Ser | Glu | Glu | Tyr | Glu | Val | Thr | Thr | Glu | Asp | Gly | Tyr | Ile |
| | | | 20 | | | | | 25 | | | | | 30 | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Leu | Val | Asn | Arg | Ile | Pro | Tyr | Gly | Arg | Thr | His | Ala | Arg | Ser | Thr |
| | | 35 | | | | | 40 | | | | | 45 | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Pro | Arg | Pro | Val | Val | Tyr | Met | Gln | His | Ala | Leu | Phe | Ala | Asp | Asn |
| | 50 | | | | | 55 | | | | | 60 | | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ala | Tyr | Trp | Leu | Glu | Asn | Tyr | Ala | Asn | Gly | Ser | Leu | Gly | Phe | Leu | Leu |
| 65 | | | | | 70 | | | | | 75 | | | | | 80 |

225

Ala Asp Ala Gly Tyr Asp Val Trp Met Gly Asn Ser Arg Gly Asn Thr
85 90 95

Trp Ser Arg Arg His Lys Thr Leu Ser Glu Thr Asp Glu Lys Phe Trp
100 105 110

Ala Phe Ser Phe Asp Glu Met Ala Lys Tyr Asp Leu Pro Gly Val Ile
115 120 125

Asp Phe Ile Val Asn Lys Thr Gly Gln Glu Lys Leu Xaa Phe Ile Gly
130 135 140

His Ser Leu Gly Thr Thr Ile Gly Phe Val Ala Phe Ser
145 150 155

<210> 398

<211> 16

<212> PRT

<213> Homo sapiens

<400> 398

Met Pro Glu Leu Ala Gln Arg Ile Lys Met Asn Phe Ala Leu Gly Pro
1 5 10 15

<210> 399

<211> 75

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (55)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (72)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 399

Phe Phe Leu Arg Gln Cys Leu Ile Leu Leu Pro Arg Leu Glu Cys Ser
1 5 10 15

Gly Met Ser Ile Thr His Cys Ser Leu Asp Leu Leu Gly Ser Ser Asn
20 25 30

Pro Pro Thr Ser Val Ser His Val Val Trp Thr Thr Gly Thr His His
35 40 45

Arg Asp Trp Leu Ile Phe Xaa Phe Phe Val Glu Met Glu Ser His Phe
50 55 60

Phe Ala Gln Ala Gly Trp Ser Xaa Leu Asn Ser
65 70 75

<210> 400

<211> 28

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

226

<222> (6)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 400

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ile | Lys | Phe | Leu | Gly | Xaa | Ser | Asp | Pro | Pro | Ile | Leu | Cys | Ser | Gln | Ser |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |

| | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ala | Gly | Ile | Thr | Gly | Met | Ser | His | Cys | Ala | His | Pro |
| | | | 20 | | | | | 25 | | | |

<210> 401

<211> 237

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (226)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 401

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Lys | Ser | Ser | Asp | Gly | Pro | Gly | Ala | Ala | Gln | Glu | Pro | Thr | Trp | Leu | Thr |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asp | Val | Pro | Ala | Ala | Met | Glu | Phe | Ile | Ala | Ala | Thr | Glu | Val | Ala | Val |
| | | | 20 | | | | | 25 | | | | | 30 | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ile | Gly | Phe | Phe | Gln | Asp | Leu | Glu | Ile | Pro | Ala | Val | Pro | Ile | Leu | His |
| | | 35 | | | | | 40 | | | | | 45 | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Met | Val | Gln | Lys | Phe | Pro | Gly | Val | Ser | Phe | Gly | Ile | Ser | Thr | Asp |
| | 50 | | | | | 55 | | | | | 60 | | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Glu | Val | Leu | Thr | His | Tyr | Asn | Ile | Thr | Gly | Asn | Thr | Ile | Cys | Leu |
| 65 | | | | | 70 | | | | | 75 | | | | | 80 |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Phe | Arg | Leu | Val | Asp | Asn | Glu | Gln | Leu | Asn | Leu | Glu | Asp | Glu | Asp | Ile |
| | | | | 85 | | | | | 90 | | | | | 95 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Glu | Ser | Ile | Asp | Ala | Thr | Lys | Leu | Ser | Arg | Phe | Ile | Glu | Ile | Asn | Ser |
| | | | 100 | | | | | 105 | | | | | 110 | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | His | Met | Val | Thr | Glu | Tyr | Asn | Pro | Val | Ala | Ser | Pro | Glu | Tyr | Glu |
| | | 115 | | | | | 120 | | | | | 125 | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Glu | Asn | Met | His | Arg | Tyr | Gln | Lys | Ala | Ala | Lys | Leu | Phe | Gln | Gly | Lys |
| | 130 | | | | | 135 | | | | | 140 | | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ile | Leu | Phe | Ile | Leu | Val | Asp | Ser | Gly | Met | Lys | Glu | Asn | Gly | Lys | Val |
| 145 | | | | | 150 | | | | | 155 | | | | | 160 |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ile | Ser | Phe | Phe | Lys | Leu | Lys | Glu | Ser | Gln | Leu | Pro | Ala | Leu | Ala | Ile |
| | | | | 165 | | | | | 170 | | | | | 175 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Tyr | Gln | Thr | Leu | Asp | Asp | Glu | Trp | Asp | Thr | Leu | Pro | Thr | Ala | Glu | Val |
| | | | 180 | | | | | 185 | | | | | 190 | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Val | Glu | His | Val | Gln | Asn | Phe | Cys | Asp | Gly | Phe | Leu | Ser | Gly | Lys |
| | | 195 | | | | | 200 | | | | | 205 | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Leu | Lys | Glu | Asn | Arg | Glu | Ser | Glu | Gly | Lys | Thr | Pro | Lys | Val | Glu |
| | 210 | | | | | 215 | | | | | 220 | | | | |

| | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Xaa | Leu | Leu | Leu | Gly | Thr | Thr | Tyr | Gly | Gln | Val | Ser |
| 225 | | | | | 230 | | | | | 235 | | |

227

<210> 402
 <211> 209
 <212> PRT
 <213> Homo sapiens

<400> 402
 Asp Gly Ala Asp Val Asn Tyr Gln Ser Lys Glu Gly Lys Ser Pro Leu
 1 5 10 15
 His Met Ala Ala Ile His Gly Arg Phe Thr Arg Ser Gln Ile Leu Ile
 20 25 30
 Gln Asn Gly Ser Glu Ile Asp Cys Ala Asp Lys Phe Gly Asn Thr Pro
 35 40 45
 Leu His Val Ala Ala Arg Tyr Gly His Glu Leu Leu Ile Ser Thr Leu
 50 55 60
 Met Thr Asn Gly Ala Asp Thr Ala Arg Arg Gly Ile His Asp Met Phe
 65 70 75 80
 Pro Leu His Leu Ala Val Leu Phe Gly Phe Ser Asp Cys Cys Arg Lys
 85 90 95
 Leu Leu Ser Ser Gly Gln Leu Tyr Ser Ile Val Ser Ser Leu Ser Asn
 100 105 110
 Glu His Val Leu Ser Ala Gly Phe Asp Ile Asn Thr Pro Asp Asn Leu
 115 120 125
 Gly Arg Thr Cys Leu His Ala Ala Ala Ser Gly Gly Asn Val Glu Cys
 130 135 140
 Leu Asn Leu Leu Leu Ser Ser Gly Ala Asp Leu Arg Arg Arg Asp Lys
 145 150 155 160
 Phe Gly Arg Thr Pro Leu His Tyr Ala Ala Ala Asn Gly Ser Tyr Gln
 165 170 175
 Cys Ala Val Thr Leu Val Thr Ala Gly Ala Gly Val Asn Glu Ala Asp
 180 185 190
 Cys Lys Gly Cys Ser Pro Leu His Tyr Ala Ala Ala Ser Asp Thr Tyr
 195 200 205

Arg

<210> 403
 <211> 192
 <212> PRT
 <213> Homo sapiens

<400> 403
 Lys Ser Pro Leu His Met Ala Ala Ile His Gly Arg Phe Thr Arg Ser
 1 5 10 15
 Gln Ile Leu Ile Gln Asn Gly Ser Glu Ile Asp Cys Ala Asp Lys Phe
 20 25 30
 Gly Asn Thr Pro Leu His Val Ala Ala Arg Tyr Gly His Glu Leu Leu
 35 40 45
 Ile Ser Thr Leu Met Thr Asn Gly Ala Asp Thr Ala Arg Arg Gly Ile
 50 55 60

228

His Asp Met Phe Pro Leu His Leu Ala Val Leu Phe Gly Phe Ser Asp
 65 70 75 80
 Cys Cys Arg Lys Leu Leu Ser Ser Gly Gln Leu Tyr Ser Ile Val Ser
 85 90 95
 Ser Leu Ser Asn Glu His Val Leu Ser Ala Gly Phe Asp Ile Asn Thr
 100 105 110
 Pro Asp Asn Leu Gly Arg Thr Cys Leu His Ala Ala Ala Ser Gly Gly
 115 120 125
 Asn Val Glu Cys Leu Asn Leu Leu Leu Ser Ser Gly Ala Asp Leu Arg
 130 135 140
 Arg Arg Asp Lys Phe Gly Arg Thr Pro Leu His Tyr Ala Ala Ala Asn
 145 150 155 160
 Gly Ser Tyr Gln Cys Ala Val Thr Leu Val Thr Ala Gly Ala Gly Val
 165 170 175
 Asn Glu Ala Asp Cys Lys Gly Cys Ser Pro Leu His Tyr Ala Ala Ala
 180 185 190

<210> 404

<211> 270

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (252)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 404

Met Gly Pro Pro Pro Gly Ala Gly Val Ser Cys Arg Gly Gly Cys Gly
 1 5 10 15
 Phe Ser Arg Leu Leu Ala Trp Cys Phe Leu Leu Ala Leu Ser Pro Gln
 20 25 30
 Ala Pro Gly Ser Arg Gly Ala Glu Ala Val Trp Thr Ala Tyr Leu Asn
 35 40 45
 Val Ser Trp Arg Val Pro His Thr Gly Val Asn Arg Thr Val Trp Glu
 50 55 60
 Leu Ser Glu Glu Gly Val Tyr Gly Gln Asp Ser Pro Leu Glu Pro Val
 65 70 75 80
 Ala Gly Val Leu Val Pro Pro Asp Gly Pro Gly Ala Leu Asn Ala Cys
 85 90 95
 Asn Pro His Thr Asn Phe Thr Val Pro Thr Val Trp Gly Ser Thr Val
 100 105 110
 Gln Val Ser Trp Leu Ala Leu Ile Gln Arg Gly Gly Gly Cys Thr Phe
 115 120 125
 Ala Asp Lys Ile His Leu Ala Tyr Glu Arg Gly Ala Ser Gly Ala Val
 130 135 140
 Ile Phe Asn Phe Pro Gly Thr Arg Asn Glu Val Ile Pro Met Ser His

229

| | | | | | | |
|-----------------|------------|-----------------|------------|-----------------|------------|-----------------|
| 145 | | 150 | | 155 | | 160 |
| Pro Gly Ala Val | Asp 165 | Ile Val Ala Ile | Met 170 | Ile Gly Asn Leu | Lys 175 | Gly |
| Thr Lys Ile | Leu 180 | Gln Ser Ile Gln | Arg 185 | Gly Ile Gln Val | Thr 190 | Met Val |
| Ile Glu Val | Gly 195 | Lys Lys His | Gly 200 | Pro Trp Val Asn | His 205 | Tyr Ser Ile |
| Phe Phe Arg | Phe 210 | Cys Val Leu | Phe 215 | Tyr Tyr Tyr | Gly 220 | Gly Asn Cys Gly |
| Leu Phe Tyr | Leu 225 | Leu Phe Cys | Ser 230 | Lys Ala Thr | Glu 235 | Cys Lys Ser Ser |
| Lys Gln Glu | Ala 245 | Glu Ala Ile | Lys 250 | Gly Arg Cys | Xaa 255 | Lys Ser Tyr Trp |
| Lys Ala Ser | Thr 260 | Thr His Thr | Glu 265 | Thr Arg Arg | Gln 270 | Gly Asn |

<210> 405

<211> 63

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (43)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 405

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Phe | Phe | Tyr | Phe | Tyr | Phe | Leu | Arg | Trp | Ser | Leu | Gly | Leu | Leu | Pro | Arg |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Glu | Cys | Ser | Gly | Thr | Ile | Ser | Ala | His | Cys | Lys | Leu | Arg | Leu | Pro |
| | | 20 | | | | | | 25 | | | | | 30 | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asp | Thr | Asn | Asn | Ser | Pro | Ala | Ser | Ala | Ser | Xaa | Val | Ala | Gly | Ile | Thr |
| | | 35 | | | | | 40 | | | | | | 45 | | |

| | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Ala | Cys | His | His | Ala | Trp | Leu | Ile | Phe | Leu | Phe | Leu | Val | Asp |
| | 50 | | | | | 55 | | | | | 60 | | | |

<210> 406

<211> 27

<212> PRT

<213> Homo sapiens

<400> 406

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Lys | Gly | Cys | Leu | Pro | Phe | Ser | Ser | Ser | Ser | Ser | Trp | Pro | Gly | Val | Pro |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |

| | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Thr | Leu | Ala | Ser | Leu | Phe | Gly | Arg | Leu | Trp | Phe |
| | | 20 | | | | | | 25 | | |

<210> 407

<211> 92

<212> PRT

<213> Homo sapiens

<400> 407

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ile | Ser | Asp | Leu | Val | Gly | Arg | Val | Val | Ser | Gly | Trp | Leu | Gly | Asp | Ala |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |

230

Val Pro Gly Pro Val Thr Arg Leu Leu Met Leu Trp Thr Thr Leu Thr
 20 25 30
 Gly Val Ser Leu Ala Leu Phe Pro Val Ala Gln Ala Pro Thr Ala Leu
 35 40 45
 Val Ala Leu Ala Val Ala Tyr Gly Phe Thr Ser Gly Ala Leu Ala Pro
 50 55 60
 Leu Ala Phe Ser Val Leu Pro Glu Leu Ile Gly Thr Arg Arg Ile Tyr
 65 70 75 80
 Cys Gly Leu Gly Leu Leu Gln Met Ile Glu Ser Ile
 85 90

<210> 408

<211> 221

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (176)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 408

Arg Phe Glu Phe Cys Glu Pro Ala Phe Val Val Gly Asn Cys Leu Gln
 1 5 10 15
 Ile Ala Ser Asp Ser His Gln Tyr Asp Arg Ile Tyr Cys Gly Ala Gly
 20 25 30
 Val Gln Lys Asp His Glu Asn Tyr Met Lys Ile Leu Leu Lys Val Gly
 35 40 45
 Gly Ile Leu Val Met Pro Ile Glu Asp Gln Leu Thr Gln Ile Met Arg
 50 55 60
 Thr Gly Gln Asn Thr Trp Glu Ser Lys Asn Ile Leu Ala Val Ser Phe
 65 70 75 80
 Ala Pro Leu Val Gln Pro Ser Lys Asn Asp Asn Gly Lys Pro Asp Ser
 85 90 95
 Val Gly Leu Pro Pro Cys Ala Val Arg Asn Leu Gln Asp Leu Ala Arg
 100 105 110
 Ile Tyr Ile Arg Arg Thr Leu Arg Asn Phe Ile Asn Asp Glu Met Gln
 115 120 125
 Ala Lys Gly Ile Pro Gln Arg Ala Pro Pro Lys Arg Lys Arg Lys Arg
 130 135 140
 Val Lys Gln Arg Ile Asn Thr Tyr Val Phe Val Gly Asn Gln Leu Ile
 145 150 155 160
 Pro Gln Pro Leu Asp Ser Glu Glu Asp Glu Lys Met Glu Glu Asp Xaa
 165 170 175
 Lys Glu Glu Glu Glu Lys Asp His Asn Glu Ala Met Lys Pro Glu Glu
 180 185 190
 Pro Pro Gln Asn Leu Leu Arg Glu Lys Ile Met Lys Leu Pro Leu Pro
 195 200 205

231

Glu Ser Leu Lys Ala Tyr Leu Thr Tyr Phe Arg Asp Lys
 210 215 220

<210> 409

<211> 137

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (136)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 409

Leu Phe Ser Cys His Arg Ser Glu Lys Thr Cys Arg Arg Trp Met Ala
 1 5 10 15

Leu Asp Tyr Ala Gly Ile Ser Ile Gly Ile Leu Gly Cys Tyr Val Ser
 20 25 30

Gly Val Phe Tyr Ala Phe Tyr Cys Asn Asn Tyr Trp Arg Gln Val Tyr
 35 40 45

Leu Ile Thr Val Leu Ala Met Ile Leu Ala Val Phe Phe Ala Gln Ile
 50 55 60

His Pro Asn Tyr Leu Thr Gln Gln Trp Gln Arg Leu Arg Ser Ile Ile
 65 70 75 80

Phe Cys Ser Val Ser Gly Tyr Gly Val Ile Pro Thr Leu His Trp Val
 85 90 95

Trp Leu Asn Gly Gly Ile Gly Ala Pro Ile Val Gln Asp Phe Ala Pro
 100 105 110

Arg Val Ile Val Met Tyr Met Ile Ala Leu Leu Ala Phe Leu Phe Tyr
 115 120 125

Ile Ser Lys Val Pro Glu Arg Xaa Phe
 130 135

<210> 410

<211> 121

<212> PRT

<213> Homo sapiens

<400> 410

Glu Thr Ala Ala Glu Tyr Val Lys Ser Arg Leu Pro Glu Ala Leu Lys
 1 5 10 15

Gln His Leu Gln Asp Tyr Glu Lys Asp Lys Glu Asn Ser Val Leu Ser
 20 25 30

Tyr Gln Thr Ile Leu Glu Gln Gln Ile Leu Ser Ile Asp Arg Glu Met
 35 40 45

Leu Glu Lys Leu Thr Val Ser Tyr Asp Glu Ala Gly Thr Thr Cys Leu
 50 55 60

Ile Ala Leu Leu Ser Asp Lys Asp Leu Thr Val Ala Asn Val Gly Asp
 65 70 75 80

Ser Arg Gly Val Leu Cys Asp Lys Asp Gly Asn Ala Ile Pro Leu Ser
 85 90 95

His Asp His Lys Pro Tyr Gln Leu Lys Glu Arg Lys Arg Ile Lys Arg

232

100 105 110

Ala Gly Gly Phe Ile Ser Phe Asn Gly
115 120

<210> 411
<211> 37
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (19)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 411
Ala His Cys Ser Leu Lys Leu Pro Gly Ser Ser His Pro Leu Ala Ser
1 5 10 15

Ala Ser Xaa Val Ala Gly Ile Thr Gly Val His His Cys His Thr Gln
20 25 30

Leu Ile Phe Asn Phe
35

<210> 412
<211> 54
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (36)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 412
Asp Thr Glu Phe His Ser Val Thr Gln Ala Gly Val Glu Trp Cys His
1 5 10 15

Leu Ser Ser Leu Gln Pro Leu Pro Pro Gly Phe Lys Gln Phe Ser Cys
20 25 30

Leu Ser Leu Xaa Ser Ser Trp Asp Tyr Arg His Val Pro Pro Cys Leu
35 40 45

Ala Asn Phe Cys Ile Phe
50

<210> 413
<211> 50
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (32)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 413
His Ser Val Thr Gln Ala Gly Val Glu Trp Cys His Leu Ser Ser Leu
1 5 10 15

Gln Pro Leu Pro Pro Gly Phe Lys Gln Phe Ser Cys Leu Ser Leu Xaa
20 25 30

Ser Ser Trp Asp Tyr Arg His Val Pro Pro Cys Leu Ala Asn Phe Cys

. 233

35 40 45
 Ile Phe
 50
 <210> 414
 <211> 94
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> SITE
 <222> (62)
 <223> Xaa equals any of the naturally occurring L-amino acids
 <400> 414
 Ser Thr His Cys Asn Leu Arg Leu Leu Gly Ser Ser Asp Ser Pro Ala
 1 5 10 15
 Ser Ala Ser Arg Val Ala Gly Val Thr Gly Met Cys His His Ala Gln
 20 25 30
 Leu Ile Phe Val Leu Leu Val Glu Thr Gly Phe Cys His Val Gly Gln
 35 40 45
 Ala Gly Leu Glu Leu Leu Thr Ser His Asp Leu Arg Thr Xaa Ala Ser
 50 55 60
 Gln Ser Val Gly Ile Thr Gly Val Ser His Arg Thr Arg Pro Gly Leu
 65 70 75 80
 Pro Leu Cys Thr Tyr Phe Val Glu Ala Glu Leu Arg Pro Gly
 85 90
 <210> 415
 <211> 34
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> SITE
 <222> (7)
 <223> Xaa equals any of the naturally occurring L-amino acids
 <220>
 <221> SITE
 <222> (23)
 <223> Xaa equals any of the naturally occurring L-amino acids
 <400> 415
 Pro Tyr Leu Pro His Phe Xaa Ile Phe Cys Arg Asp Gly Val Ser Leu
 1 5 10 15
 Cys Cys Pro Gly Trp Ser Xaa Thr Pro Glu Phe Lys Gln Ser Ser Ala
 20 25 30
 Leu Ala
 <210> 416
 <211> 13
 <212> PRT
 <213> Homo sapiens
 <400> 416
 Glu Cys Trp Asp Tyr Arg His Glu Pro Ser Cys Leu Ala

234

1 5 10
 <210> 417
 <211> 7
 <212> PRT
 <213> Homo sapiens

 <400> 417
 Leu Pro Lys Cys Trp Ser Ala
 1 5

 <210> 418
 <211> 317
 <212> PRT
 <213> Homo sapiens

 <400> 418
 Val Ala Val Leu Cys Val Cys Asp Leu Ser Pro Ala Gln Cys Asp Ile
 1 5 10 15

 Asn Cys Cys Cys Asp Pro Asp Cys Ser Ser Val Asp Phe Ser Val Phe
 20 25 30

 Ser Ala Cys Ser Val Pro Val Val Thr Gly Asp Ser Gln Phe Cys Ser
 35 40 45

 Gln Lys Ala Val Ile Tyr Ser Leu Asn Phe Thr Ala Asn Pro Pro Gln
 50 55 60

 Arg Val Phe Glu Leu Val Asp Gln Ile Asn Pro Ser Ile Phe Cys Ile
 65 70 75 80

 His Ile Thr Asn Tyr Lys Pro Ala Leu Ser Phe Ile Asn Pro Glu Val
 85 90 95

 Pro Asp Glu Asn Asn Phe Asp Thr Leu Met Lys Thr Ser Asp Gly Phe
 100 105 110

 Thr Leu Asn Ala Glu Ser Tyr Val Ser Phe Thr Thr Lys Leu Asp Ile
 115 120 125

 Pro Thr Ala Ala Lys Tyr Glu Tyr Gly Val Pro Leu Gln Thr Ser Asp
 130 135 140

 Ser Phe Leu Arg Phe Pro Ser Ser Leu Thr Ser Ser Leu Cys Thr Asp
 145 150 155 160

 Asn Asn Pro Ala Ala Phe Leu Val Asn Gln Ala Val Lys Cys Thr Arg
 165 170 175

 Lys Ile Asn Leu Glu Gln Cys Glu Glu Ile Glu Ala Leu Ser Met Ala
 180 185 190

 Phe Tyr Ser Ser Pro Glu Ile Leu Arg Val Pro Asp Ser Arg Lys Lys
 195 200 205

 Val Pro Ile Thr Val Gln Ser Ile Val Ile Gln Ser Leu Asn Lys Thr
 210 215 220

 Leu Thr Arg Arg Glu Asp Thr Asp Val Leu Gln Pro Thr Leu Val Asn
 225 230 235 240

 Ala Gly His Phe Ser Leu Cys Val Asn Val Val Leu Glu Val Lys Tyr
 245 250 255

 Ser Leu Thr Tyr Thr Asp Ala Gly Glu Val Thr Lys Ala Asp Leu Ser

235

| | | |
|---|-----|-----|
| 260 | 265 | 270 |
| Phe Val Leu Gly Thr Val Ser Ser Val Val Val Pro Leu Gln Gln Lys | | |
| 275 | 280 | 285 |
| Phe Glu Ile His Phe Leu Gln Glu Asn Thr Gln Pro Val Pro Leu Ser | | |
| 290 | 295 | 300 |
| Gly Asn Pro Gly Tyr Val Val Gly Leu Pro Leu Ala Ala | | |
| 305 | 310 | 315 |

<210> 419

<211> 118

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (9)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (91)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 419

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Cys | Leu | Leu | His | Pro | Ile | Ile | Pro | Xaa | Pro | Val | Ile | Asn | Gly | Tyr | Arg |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asn | Lys | Ser | Thr | Phe | Ser | Val | Asn | Arg | Gly | Pro | Asp | Gly | Asn | Pro | Lys |
| | | | 20 | | | | | 25 | | | | | 30 | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Thr | Val | Gly | Phe | Tyr | Leu | Gly | Thr | Trp | Arg | Asp | Gly | Asn | Val | Val | Cys |
| | | 35 | | | | | 40 | | | | | 45 | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Gln | Ser | Asn | His | Leu | Lys | Asn | Ile | Pro | Glu | Lys | His | Ser | Gln | Val |
| 50 | | | | | | 55 | | | | | 60 | | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ala | Gln | Tyr | Tyr | Glu | Val | Phe | Leu | Arg | Gln | Ser | Pro | Leu | Glu | Pro | Cys |
| 65 | | | | | 70 | | | | | 75 | | | | | 80 |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Val | Phe | His | Glu | Gly | Gly | Tyr | Trp | Arg | Xaa | Leu | Thr | Val | Arg | Thr |
| | | | 85 | | | | | | 90 | | | | | 95 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asn | Ser | Gln | Gly | His | Thr | Met | Ala | Ile | Ile | Thr | Phe | His | Pro | Gln | Lys |
| | | | 100 | | | | | 105 | | | | | 110 | | |

| | | | | | |
|-----|-----|-----|-----|-----|-----|
| Leu | Ser | Gln | Glu | Glu | Leu |
| | | 115 | | | |

<210> 420

<211> 15

<212> PRT

<213> Homo sapiens

<400> 420

| | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Pro | Gly | Ala | Ala | Cys | Gly | Leu | Thr | Ser | Leu | Tyr | Phe | Gln | Glu |
| 1 | | | | 5 | | | | | 10 | | | | | 15 |

<210> 421

<211> 54

<212> PRT

<213> Homo sapiens

<400> 421

236

Gly Trp Gln Ala Leu Arg Glu Glu Ser His Cys Thr Ala Ser Asp Thr
 1 5 10 15
 Ser Ser Pro Trp Trp Val Ser Ser Pro Asn Gln Asp Cys Phe Pro Gly
 20 25 30
 Met Pro Glu Ile His Gln Asp Gly His Ser Ser Phe Trp Ala Gln Tyr
 35 40 45
 Val Arg Glu Ile Ser Pro
 50

<210> 422
 <211> 191
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (130)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 422
 Asn Cys Gln Glu Met Ser Asn Thr Asn Gly Ser Ala Ile Thr Glu Phe
 1 5 10 15
 Ile Leu Leu Gly Leu Thr Asp Cys Pro Glu Leu Gln Ser Leu Leu Phe
 20 25 30
 Val Leu Phe Leu Val Val Tyr Leu Val Thr Leu Leu Gly Asn Leu Gly
 35 40 45
 Met Ile Met Leu Met Arg Leu Asp Ser Arg Leu His Thr Pro Met Tyr
 50 55 60
 Phe Phe Leu Thr Asn Leu Ala Phe Val Asp Leu Cys Tyr Thr Ser Asn
 65 70 75 80
 Ala Thr Pro Gln Met Ser Thr Asn Ile Val Ser Glu Lys Thr Ile Ser
 85 90 95
 Phe Ala Gly Cys Phe Thr Gln Cys Tyr Ile Phe Ile Ala Leu Leu Leu
 100 105 110
 Thr Glu Phe Tyr Met Leu Ala Ala Met Ala Tyr Asp Arg Tyr Val Ala
 115 120 125
 Ile Xaa Asp Pro Leu Arg Tyr Ser Val Lys Thr Ser Arg Arg Val Cys
 130 135 140
 Ile Cys Leu Ala Thr Phe Pro Tyr Val Tyr Gly Phe Ser Asp Gly Leu
 145 150 155 160
 Phe Gln Ala Ile Leu Thr Phe Arg Leu Thr Phe Cys Arg Ser Asn Val
 165 170 175
 Ile Asn His Phe Tyr Cys Ala Asp Pro Pro Leu Ile Lys Leu Ser
 180 185 190

<210> 423
 <211> 110
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE

237

<222> (65)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (90)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (97)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (103)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 423

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asp | Ile | Cys | Gly | Ser | Arg | Asn | Ser | Cys | Val | Ser | Cys | Val | Asp | Gly | Asn |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ala | Thr | Cys | Phe | Trp | Ile | Glu | Cys | Lys | Gly | Lys | Ser | Tyr | Cys | Ser | Asp |
| | | | 20 | | | | | 25 | | | | | 30 | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asn | Ser | Thr | Ala | Gly | Asp | Cys | Lys | Val | Val | Asn | Thr | Thr | Gly | Phe | Cys |
| | | 35 | | | | | 40 | | | | | 45 | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Ala | Lys | Thr | Thr | Thr | Leu | Pro | Ser | Thr | Thr | Thr | Thr | Ser | Thr | Thr |
| | 50 | | | | | 55 | | | | | 60 | | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Xaa | Thr | Thr | Ser | Gly | Thr | Thr | Asn | Thr | Thr | Leu | Ser | Pro | Thr | Ile | Gln |
| 65 | | | | | 70 | | | | | 75 | | | | | 80 |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Pro | Thr | Arg | Lys | Ser | Thr | Phe | Asp | Ala | Xaa | Gln | Phe | His | Trp | Arg | Asn |
| | | | 85 | | | | | | 90 | | | | | 95 | |

| | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Xaa | Pro | Cys | Leu | Gly | Val | Xaa | Ala | Val | Ile | Phe | Phe | Leu | Tyr |
| | | 100 | | | | | | 105 | | | | | 110 |

<210> 424

<211> 146

<212> PRT

<213> Homo sapiens

<400> 424

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Lys | Lys | Thr | Trp | Ala | Arg | Trp | Arg | His | Met | Phe | Arg | Glu | Gln | Pro |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Asp | Glu | Ile | Arg | Asn | Tyr | Phe | Gly | Glu | Lys | Val | Ala | Leu | Tyr | Phe |
| | | | 20 | | | | | 25 | | | | | 30 | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Trp | Leu | Gly | Trp | Tyr | Thr | Tyr | Met | Leu | Val | Pro | Ala | Ala | Leu | Thr |
| | | 35 | | | | | 40 | | | | | 45 | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Leu | Leu | Val | Phe | Leu | Ser | Gly | Phe | Ser | Leu | Phe | Glu | Ala | Ser | Gln |
| | 50 | | | | | 55 | | | | | 60 | | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ile | Ser | Lys | Glu | Ile | Cys | Glu | Ala | His | Asp | Ile | Leu | Met | Cys | Pro | Leu |
| 65 | | | | | 70 | | | | | 75 | | | | | 80 |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Asp | His | Ser | Arg | Arg | Tyr | Gln | Arg | Leu | Ser | Glu | Thr | Cys | Thr | Phe |
| | | | | 85 | | | | | 90 | | | | | 95 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ala | Lys | Leu | Thr | His | Leu | Phe | Asp | Asn | Asp | Gly | Thr | Val | Val | Phe | Ala |
| | | | 100 | | | | | 105 | | | | | 110 | | |

238

Ile Phe Met Ala Leu Trp Ala Thr Val Phe Leu Glu Ile Trp Lys Arg
 115 120 125

Gln Arg Ala Arg Val Val Leu His Trp Asp Leu Tyr Val Trp Asp Glu
 130 135 140

Glu Gln
 145

<210> 425

<211> 44

<212> PRT

<213> Homo sapiens

<400> 425

Met Glu Ser Arg Ser Val Ser Gln Ala Gly Gly Gln Trp Arg Asp Leu
 1 5 10 15

Gly Ser Leu Gln Pro Pro Pro Pro Arg Phe Lys Arg Phe Ser Cys Leu
 20 25 30

Gly Leu Pro Lys Cys Trp Asp Tyr Arg His Glu Pro
 35 40

<210> 426

<211> 40

<212> PRT

<213> Homo sapiens

<400> 426

Ser Val Ser Gln Ala Gly Gly Gln Trp Arg Asp Leu Gly Ser Leu Gln
 1 5 10 15

Pro Pro Pro Pro Arg Phe Lys Arg Phe Ser Cys Leu Gly Leu Pro Lys
 20 25 30

Cys Trp Asp Tyr Arg His Glu Pro
 35 40

<210> 427

<211> 66

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (28)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (39)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 427

Pro Arg Leu Lys Gln Ser Phe Cys Leu Asp Leu Pro Arg Cys Trp Asp
 1 5 10 15

Tyr Arg His Glu Pro Leu His Leu Ala Phe Ile Xaa Phe Leu Ser Phe
 20 25 30

Phe Leu Ser Phe Phe Phe Xaa Met Glu Ser Arg Ser Val Ser Gln Ala
 35 40 45

Gly Gly Gln Trp Arg Asp Leu Gly Ser Leu Gln Pro Pro Pro Pro Arg

239

50 55 60
 Phe Lys
 65
 <210> 428
 <211> 44
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> SITE
 <222> (7)
 <223> Xaa equals any of the naturally occurring L-amino acids
 <400> 428
 Ala Gln Ala Gly Val Gln Xaa Leu Asn Leu Ser Ser Leu Gln Pro Gln
 1 5 10 15
 Pro Ala Gly Leu Lys Gln Ser Ser His Pro Ser Leu Pro Ser Ser Trp
 20 25 30
 Asp Tyr Arg Tyr Ser Thr Pro His Pro Ala Asn Phe
 35 40
 <210> 429
 <211> 31
 <212> PRT
 <213> Homo sapiens
 <400> 429
 Phe Phe Cys Arg Asp Gly Ile Ser Pro Cys Cys Pro Gly Trp Ser Arg
 1 5 10 15
 Thr Pro Arg Leu Arg Arg Ser Ala His Leu Asn Leu Pro Gln Cys
 20 25 30
 <210> 430
 <211> 356
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> SITE
 <222> (189)
 <223> Xaa equals any of the naturally occurring L-amino acids
 <220>
 <221> SITE
 <222> (253)
 <223> Xaa equals any of the naturally occurring L-amino acids
 <400> 430
 Met Phe Gly Thr Leu Leu Leu Tyr Cys Phe Phe Leu Ala Thr Val Pro
 1 5 10 15
 Ala Leu Ala Glu Thr Gly Gly Glu Arg Gln Leu Ser Pro Glu Lys Ser
 20 25 30
 Glu Ile Trp Gly Pro Gly Leu Lys Ala Asp Val Val Leu Pro Ala Arg
 35 40 45
 Tyr Phe Tyr Ile Gln Ala Val Asp Thr Ser Gly Asn Lys Phe Thr Ser
 50 55 60
 Ser Pro Gly Glu Lys Val Phe Gln Val Lys Val Ser Ala Pro Glu Glu

240

| 65 | | | | | 70 | | | | | 75 | | | | | 80 |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gln | Phe | Thr | Arg | Val | Gly | Val | Gln | Val | Leu | Asp | Arg | Lys | Asp | Gly | Ser |
| | | | | 85 | | | | | 90 | | | | | 95 | |
| Phe | Ile | Val | Arg | Tyr | Arg | Met | Tyr | Ala | Ser | Tyr | Lys | Asn | Leu | Lys | Val |
| | | | 100 | | | | | 105 | | | | | 110 | | |
| Glu | Val | Lys | Phe | Gln | Gly | Gln | His | Val | Ala | Lys | Ser | Pro | Tyr | Ile | Leu |
| | | 115 | | | | | 120 | | | | | 125 | | | |
| Lys | Gly | Pro | Val | Tyr | His | Glu | Asn | Cys | Asp | Cys | Pro | Leu | Gln | Asp | Ser |
| | 130 | | | | | 135 | | | | | 140 | | | | |
| Ala | Ala | Trp | Leu | Arg | Glu | Met | Asn | Cys | Pro | Glu | Thr | Ile | Ala | Gln | Ile |
| 145 | | | | | 150 | | | | | 155 | | | | | 160 |
| Gln | Arg | Asp | Leu | Ala | His | Phe | Pro | Ala | Val | Asp | Pro | Glu | Lys | Ile | Ala |
| | | | | 165 | | | | | 170 | | | | | 175 | |
| Val | Glu | Ile | Pro | Lys | Arg | Phe | Gly | Gln | Arg | Gln | Ser | Xaa | Cys | His | Tyr |
| | | | 180 | | | | | 185 | | | | | 190 | | |
| Thr | Leu | Lys | Asp | Asn | Lys | Val | Tyr | Ile | Lys | Thr | His | Gly | Glu | His | Val |
| | | 195 | | | | | 200 | | | | | 205 | | | |
| Gly | Phe | Arg | Ile | Phe | Met | Asp | Ala | Ile | Leu | Leu | Ser | Leu | Thr | Arg | Lys |
| | 210 | | | | | 215 | | | | | 220 | | | | |
| Val | Lys | Met | Pro | Asp | Val | Glu | Leu | Phe | Val | Asn | Leu | Gly | Asp | Trp | Pro |
| 225 | | | | | 230 | | | | | 235 | | | | | 240 |
| Leu | Glu | Lys | Lys | Lys | Ser | Asn | Ser | Asn | Ile | His | Pro | Xaa | Phe | Ser | Trp |
| | | | | 245 | | | | | 250 | | | | | 255 | |
| Cys | Gly | Ser | Thr | Asp | Ser | Lys | Asp | Ile | Val | Met | Pro | Thr | Tyr | Asp | Leu |
| | | | 260 | | | | | 265 | | | | | 270 | | |
| Thr | Asp | Ser | Val | Leu | Glu | Thr | Met | Gly | Arg | Val | Ser | Leu | Asp | Met | Met |
| | | 275 | | | | | 280 | | | | | 285 | | | |
| Ser | Val | Gln | Ala | Asn | Thr | Gly | Pro | Pro | Trp | Glu | Ser | Lys | Asn | Ser | Thr |
| | 290 | | | | | 295 | | | | | 300 | | | | |
| Ala | Val | Trp | Arg | Gly | Arg | Asp | Ser | Arg | Lys | Glu | Arg | Leu | Glu | Leu | Val |
| 305 | | | | | 310 | | | | | 315 | | | | | 320 |
| Lys | Leu | Ser | Arg | Lys | His | Pro | Glu | Leu | Ile | Asp | Ala | Ala | Phe | Thr | Asn |
| | | | | 325 | | | | | 330 | | | | | 335 | |
| Phe | Phe | Phe | Phe | Lys | His | Asp | Glu | Asn | Leu | Tyr | Gly | Pro | Ile | Val | Asn |
| | | | 340 | | | | | 345 | | | | | 350 | | |
| Ile | Phe | His | Phe | | | | | | | | | | | | |
| | | | 355 | | | | | | | | | | | | |

<210> 431

<211> 151

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (14)

<223> Xaa equals any of the naturally occurring L-amino acids

241

<220>

<221> SITE

<222> (70)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 431

Glu His Ile Ser Phe Phe Asp Phe Phe Lys His Lys Tyr Xaa Ile Asn
 1 5 10 15

Ile Asp Gly Thr Val Ala Ala Tyr Arg Leu Pro Tyr Leu Leu Val Gly
 20 25 30

Asp Ser Val Val Leu Lys Gln Asp Ser Ile Tyr Tyr Glu His Phe Tyr
 35 40 45

Asn Glu Leu Gln Pro Trp Lys His Tyr Ile Pro Val Lys Ser Asn Leu
 50 55 60

Ser Asp Leu Leu Glu Xaa Leu Lys Trp Ala Lys Asp His Asp Glu Glu
 65 70 75 80

Ala Lys Lys Ile Ala Lys Ala Gly Gln Glu Phe Ala Arg Asn Asn Leu
 85 90 95

Met Gly Asp Asp Ile Phe Cys Tyr Tyr Phe Lys Leu Phe Gln Glu Tyr
 100 105 110

Ala Asn Leu Gln Val Ser Glu Pro Gln Ile Arg Glu Gly Met Lys Arg
 115 120 125

Val Glu Pro Gln Thr Glu Asp Asp Leu Phe Pro Cys Thr Cys His Arg
 130 135 140

Lys Lys Thr Lys Asp Glu Leu
 145 150

<210> 432

<211> 158

<212> PRT

<213> Homo sapiens

<400> 432

Asp Trp Leu Thr Glu Lys Pro Glu Leu Phe Gln Leu Ala Leu Lys Ala
 1 5 10 15

Phe Arg Tyr Thr Leu Lys Leu Met Ile Asp Lys Ala Ser Leu Gly Pro
 20 25 30

Ile Glu Asp Phe Arg Glu Leu Ile Lys Tyr Leu Glu Glu Tyr Glu Arg
 35 40 45

Asp Trp Tyr Ile Gly Leu Val Ser Asp Glu Lys Trp Lys Glu Ala Ile
 50 55 60

Leu Gln Glu Lys Pro Tyr Leu Phe Ser Leu Gly Tyr Asp Ser Asn Met
 65 70 75 80

Gly Ile Tyr Thr Gly Arg Val Leu Ser Leu Gln Glu Leu Leu Ile Gln
 85 90 95

Val Gly Lys Leu Asn Pro Glu Ala Val Arg Gly Gln Trp Ala Asn Leu
 100 105 110

Ser Trp Glu Leu Leu Tyr Ala Thr Asn Asp Asp Glu Glu Arg Tyr Ser
 115 120 125

242

Ile Gln Ala His Pro Leu Leu Leu Arg Asn Leu Thr Val Gln Ala Ala
 130 135 140

Glu Pro Pro Leu Gly Tyr Pro Ile Tyr Ser Ser Lys Pro Leu
 145 150 155

<210> 433

<211> 120

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (64)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 433

Val Arg Met Glu Met Ala Ser Ser Ala Gly Ser Trp Leu Ser Gly Cys
 1 5 10 15

Leu Ile Pro Leu Val Phe Leu Arg Leu Ser Val His Val Ser Gly His
 20 25 30

Ala Gly Asp Ala Gly Lys Phe His Val Ala Leu Leu Gly Gly Thr Ala
 35 40 45

Glu Leu Leu Cys Pro Leu Ser Leu Trp Pro Gly Thr Val Pro Lys Xaa
 50 55 60

Val Arg Trp Leu Arg Ser Pro Phe Pro Gln Arg Ser Gln Ala Val His
 65 70 75 80

Ile Phe Arg Asp Gly Lys Asp Gln Asp Glu Asp Leu Met Pro Glu Tyr
 85 90 95

Lys Gly Arg Thr Val Leu Val Arg Asp Ala Gln Glu Gly Ser Val Thr
 100 105 110

Leu Gln Ile Leu Asp Val Arg Leu
 115 120

<210> 434

<211> 143

<212> PRT

<213> Homo sapiens

<400> 434

Asp Pro His Gln Leu Phe Asp Asp Thr Ser Ser Ala Gln Ser Arg Gly
 1 5 10 15

Tyr Gly Ala Gln Arg Ala Pro Gly Gly Leu Ser Tyr Pro Ala Ala Ser
 20 25 30

Pro Thr Pro His Ala Ala Phe Leu Ala Asp Pro Val Ser Asn Met Ala
 35 40 45

Met Ala Tyr Gly Ser Ser Leu Ala Ala Gln Gly Lys Glu Leu Val Asp
 50 55 60

Lys Asn Ile Asp Arg Phe Ile Pro Ile Thr Lys Leu Lys Tyr Tyr Phe
 65 70 75 80

Ala Val Asp Thr Met Tyr Val Gly Arg Lys Leu Gly Leu Leu Phe Phe
 85 90 95

Pro Tyr Leu His Gln Asp Trp Glu Val Gln Tyr Gln Gln Asp Thr Pro

243

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| | 100 | | 105 | | 110 | | | | | | | | | | |
| Val | Ala | Pro | Arg | Phe | Asp | Val | Asn | Ala | Pro | Asp | Leu | Tyr | Ile | Pro | Ala |
| | 115 | | | | | | 120 | | | | | 125 | | | |
| Met | Ala | Phe | Ile | Thr | Tyr | Val | Leu | Val | Ala | Gly | Leu | Arg | Trp | Gly | |
| | 130 | | | | | | 135 | | | | 140 | | | | |

<210> 435

<211> 179

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (102)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (160)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 435

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Asn | Met | Ser | Val | Leu | Thr | Leu | Gln | Glu | Tyr | Glu | Phe | Glu | Lys | Gln |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Phe | Asn | Glu | Asn | Glu | Ala | Ile | Gln | Trp | Met | Gln | Glu | Asn | Trp | Lys | Lys |
| | | | 20 | | | | | 25 | | | | | 30 | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Phe | Leu | Phe | Ser | Ala | Leu | Tyr | Ala | Ala | Phe | Ile | Phe | Gly | Gly | Arg |
| | | 35 | | | | | 40 | | | | | 45 | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| His | Leu | Met | Asn | Lys | Arg | Ala | Lys | Phe | Glu | Leu | Arg | Lys | Pro | Leu | Val |
| | 50 | | | | | 55 | | | | | 60 | | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Trp | Ser | Leu | Thr | Leu | Ala | Val | Phe | Ser | Ile | Phe | Gly | Ala | Leu | Arg |
| 65 | | | | | 70 | | | | | 75 | | | | | 80 |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Thr | Gly | Ala | Tyr | Met | Val | Tyr | Ile | Leu | Met | Thr | Lys | Gly | Leu | Lys | Gln |
| | | | | 85 | | | | | 90 | | | | | 95 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Val | Cys | Asp | Gln | Xaa | Phe | Tyr | Asn | Gly | Pro | Val | Ser | Lys | Phe | Trp |
| | | | 100 | | | | | 105 | | | | | 110 | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ala | Tyr | Ala | Phe | Val | Leu | Ser | Lys | Ala | Pro | Glu | Leu | Gly | Asp | Thr | Ile |
| | | 115 | | | | | 120 | | | | | 125 | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Phe | Ile | Ile | Leu | Arg | Lys | Gln | Lys | Leu | Ile | Phe | Leu | His | Trp | Tyr | His |
| | 130 | | | | | 135 | | | | | 140 | | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| His | Ile | Thr | Val | Leu | Leu | Tyr | Ser | Trp | Tyr | Ser | Tyr | Lys | Asp | Met | Xaa |
| 145 | | | | | 150 | | | | | 155 | | | | | 160 |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Cys | Arg | Gly | Gly | Trp | Phe | Met | Thr | Met | Asn | Tyr | Gly | Val | His | Ala | Val |
| | | | | 165 | | | | | 170 | | | | | 175 | |

Met Tyr Ser

<210> 436

<211> 98

<212> PRT

<213> Homo sapiens

<400> 436

244

Arg Trp Asn Phe Ser Leu Ile Ala Gln Ala Gly Val Gln Trp His Asp
 1 5 10 15
 Leu Gly Ser Pro Gln Pro Pro Pro Pro Gly Leu Lys Arg Phe Ser Phe
 20 25 30
 Leu Gly Leu Pro Ser Ser Trp Asp Tyr Arg His Ala Pro Pro Cys Pro
 35 40 45
 Ala Asn Phe Val Phe Leu Val Glu Met Gly Phe Leu His Val Gly Gln
 50 55 60
 Ala Gly Leu Glu Leu Pro Thr Ser Gly Gly Pro Pro Ala Trp Ala Ser
 65 70 75 80
 Gln Ser Ala Gly Ile Thr Gly Val Ser His Arg Ala Trp Pro Glu Asn
 85 90 95
 Ser His

<210> 437
 <211> 583
 <212> PRT
 <213> Homo sapiens

<400> 437
 Val Thr Arg Gln Asp Met Asn Asp Ala Val Ile Thr Leu Asn Gly Leu
 1 5 10 15
 Glu Lys Arg Phe Pro Gly Met Asp Lys Pro Ala Val Ala Pro Leu Asp
 20 25 30
 Cys Thr Ile His Ala Gly Tyr Val Thr Gly Leu Val Gly Pro Asp Gly
 35 40 45
 Ala Gly Lys Thr Thr Leu Met Arg Met Leu Ala Gly Leu Leu Lys Pro
 50 55 60
 Asp Ser Gly Ser Ala Thr Val Ile Gly Phe Asp Pro Ile Lys Asn Asp
 65 70 75 80
 Gly Ala Leu His Ala Val Leu Gly Tyr Met Pro Gln Lys Phe Gly Leu
 85 90 95
 Tyr Glu Asp Leu Thr Val Met Glu Asn Leu Asn Leu Tyr Ala Asp Leu
 100 105 110
 Arg Ser Val Thr Gly Glu Ala Arg Lys Gln Thr Phe Ala Arg Leu Leu
 115 120 125
 Glu Phe Thr Ser Leu Gly Pro Phe Thr Gly Arg Leu Ala Gly Lys Leu
 130 135 140
 Ser Gly Gly Met Lys Gln Lys Leu Gly Leu Ala Cys Thr Leu Val Gly
 145 150 155 160
 Glu Pro Lys Val Leu Leu Leu Asp Glu Pro Gly Val Gly Val Asp Pro
 165 170 175
 Ile Ser Arg Arg Glu Leu Trp Gln Met Val His Glu Leu Ala Gly Glu
 180 185 190
 Gly Met Leu Ile Leu Trp Ser Thr Ser Tyr Leu Asp Glu Ala Glu Gln
 195 200 205

245

| | | | | | | | | | | | | | | | |
|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| Cys 210 | Arg | Asp | Val | Leu | Leu | Met 215 | Asn | Glu | Gly | Glu | Leu 220 | Leu | Tyr | Gln | Gly |
| Glu 225 | Pro | Lys | Ala | Leu | Thr 230 | Gln | Thr | Met | Ala | Gly 235 | Arg | Ser | Phe | Leu | Met 240 |
| Thr | Ser | Pro | His | Glu 245 | Gly | Asn | Arg | Lys | Leu 250 | Leu | Gln | Arg | Ala | Leu 255 | Lys |
| Leu | Pro | Gln | Val 260 | Ser | Asp | Gly | Met | Ile 265 | Gln | Gly | Lys | Ser | Val 270 | Arg | Leu |
| Ile | Leu | Lys 275 | Lys | Glu | Ala | Thr | Pro 280 | Asp | Asp | Ile | Arg | His 285 | Ala | Asp | Gly |
| Met | Pro 290 | Glu | Ile | Asn | Ile | Asn 295 | Glu | Thr | Thr | Pro | Arg 300 | Phe | Glu | Asp | Ala |
| Phe 305 | Ile | Asp | Leu | Leu | Gly 310 | Gly | Ala | Gly | Thr | Ser 315 | Glu | Ser | Pro | Leu | Gly 320 |
| Ala | Ile | Leu | His | Thr 325 | Val | Glu | Gly | Thr | Pro 330 | Gly | Glu | Thr | Val | Ile 335 | Glu |
| Ala | Lys | Glu | Leu 340 | Thr | Lys | Lys | Phe | Gly 345 | Asp | Phe | Ala | Ala | Thr 350 | Asp | His |
| Val | Asn | Phe 355 | Ala | Val | Lys | Arg | Gly 360 | Glu | Ile | Phe | Gly | Leu 365 | Leu | Gly | Pro |
| Asn | Gly 370 | Ala | Gly | Lys | Ser | Thr 375 | Thr | Phe | Lys | Met | Met 380 | Cys | Gly | Leu | Leu |
| Val 385 | Pro | Thr | Ser | Gly | Gln 390 | Ala | Leu | Val | Leu | Gly 395 | Met | Asp | Leu | Lys | Glu 400 |
| Ser | Ser | Gly | Lys | Ala 405 | Arg | Gln | His | Leu | Gly 410 | Tyr | Met | Ala | Gln | Lys 415 | Phe |
| Ser | Leu | Tyr | Gly 420 | Asn | Leu | Thr | Val | Glu 425 | Gln | Asn | Leu | Arg | Phe 430 | Phe | Ser |
| Gly | Val | Tyr 435 | Gly | Leu | Arg | Gly | Arg 440 | Ala | Gln | Asn | Glu | Lys 445 | Ile | Ser | Arg |
| Met | Ser 450 | Glu | Ala | Phe | Gly | Leu 455 | Lys | Ser | Ile | Ala | Ser 460 | His | Ala | Thr | Asp |
| Glu 465 | Leu | Pro | Leu | Gly | Phe 470 | Lys | Gln | Arg | Leu | Ala 475 | Leu | Ala | Cys | Ser | Leu 480 |
| Met | His | Glu | Pro | Asp 485 | Ile | Leu | Phe | Leu | Asp 490 | Glu | Pro | Thr | Ser | Gly 495 | Val |
| Asp | Pro | Leu | Thr 500 | Arg | Arg | Glu | Phe | Trp 505 | Leu | His | Ile | Asn | Ser 510 | Met | Val |
| Glu | Lys | Gly 515 | Val | Thr | Val | Met | Val 520 | Thr | Thr | His | Phe | Met 525 | Asp | Glu | Ala |
| Glu | Tyr 530 | Cys | Asp | Arg | Ile | Gly 535 | Leu | Val | Tyr | Arg | Gly 540 | Lys | Leu | Ile | Ala |
| Ser 545 | Gly | Thr | Pro | Asp | Asp 550 | Leu | Lys | Ala | Gln | Ser 555 | Ala | Asn | Asp | Glu | Gln 560 |

246

Pro Asp Pro Thr Met Glu Gln Ala Phe Ile Gln Leu Ile His Asp Trp
 565 570 575

Asp Lys Glu His Ser Asn Glu
 580

<210> 438

<211> 72

<212> PRT

<213> Homo sapiens

<400> 438

Ser Ile Glu Leu Leu Gly Ser Asp Asp Leu Ser Thr Ser Ala Ser Gln
 1 5 10 15

Val Val Gly Thr Leu Gly Met Leu Cys His Ala Trp Leu Leu Leu Met
 20 25 30

Tyr Leu Phe Leu Glu Met Arg Ser His Cys Val Ala Gln Thr Gly Leu
 35 40 45

Glu Leu Leu Ala Ser Ser His Pro Pro Phe Ser Ala Ser Thr Val Ala
 50 55 60

Gly Ile Ser Gly Thr Cys His Cys
 65 70

<210> 439

<211> 143

<212> PRT

<213> Homo sapiens

<400> 439

Asp Pro His Gln Leu Phe Asp Asp Thr Ser Ser Ala Gln Ser Arg Gly
 1 5 10 15

Tyr Gly Ala Gln Arg Ala Pro Gly Gly Leu Ser Tyr Pro Ala Ala Ser
 20 25 30

Pro Thr Pro His Ala Ala Phe Leu Ala Asp Pro Val Ser Asn Met Ala
 35 40 45

Met Ala Tyr Gly Ser Ser Leu Ala Ala Gln Gly Lys Glu Leu Val Asp
 50 55 60

Lys Asn Ile Asp Arg Phe Ile Pro Ile Thr Lys Leu Lys Tyr Tyr Phe
 65 70 75 80

Ala Val Asp Thr Met Tyr Val Gly Arg Lys Leu Gly Leu Leu Phe Phe
 85 90 95

Pro Tyr Leu His Gln Asp Trp Glu Val Gln Tyr Gln Gln Asp Thr Pro
 100 105 110

Val Ala Pro Arg Phe Asp Val Asn Ala Pro Asp Leu Tyr Ile Pro Ala
 115 120 125

Met Ala Phe Ile Thr Tyr Val Leu Val Ala Gly Leu Arg Trp Gly
 130 135 140

<210> 440

<211> 234

<212> PRT

<213> Homo sapiens

<220>

247

<221> SITE
 <222> (10)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <220>
 <221> SITE
 <222> (93)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <220>
 <221> SITE
 <222> (95)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <220>
 <221> SITE
 <222> (101)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <400> 440
 Gly Pro Ala Pro Cys Pro Thr Leu Gly Xaa Ser Cys Cys Cys Ser Cys
 1 5 10 15
 Cys Cys Cys Pro Ser Gly Ala Lys Pro Thr Gln Ala Ala Thr Gly Ser
 20 25 30
 Gln Gly Cys Pro Ala Cys Pro Gly His Gln Gly Arg Met Gly Thr Thr
 35 40 45
 Asp Cys Arg Gly Pro Arg Gly Ser Gln Glu Ser Gln Pro Phe Pro Gly
 50 55 60
 Ser Glu Asp Pro Lys Gly Arg Arg Glu Asn Pro Ala Tyr Pro Ala Ile
 65 70 75 80
 Leu Gly Lys Met Ala Pro Trp Asp Pro Leu Gly Cys Xaa Gly Xaa Pro
 85 90 95
 Ala Pro Trp Ala Xaa Leu Glu Ser Gln Lys Phe Gln Ser Val Phe Thr
 100 105 110
 Val Thr Arg Gln Thr His Gln Pro Pro Ala Pro Asn Ser Leu Ile Arg
 115 120 125
 Phe Asn Ala Val Leu Thr Asn Pro Gln Gly Asp Tyr Asp Thr Ser Thr
 130 135 140
 Gly Lys Phe Thr Cys Lys Val Pro Gly Leu Tyr Tyr Phe Val Tyr His
 145 150 155 160
 Ala Ser His Thr Ala Asn Leu Cys Val Leu Leu Tyr Arg Ser Gly Val
 165 170 175
 Lys Val Val Thr Phe Cys Gly His Thr Ser Lys Thr Asn Gln Val Asn
 180 185 190
 Ser Gly Gly Val Leu Leu Arg Leu Gln Val Gly Glu Glu Val Trp Leu
 195 200 205
 Ala Val Asn Asp Tyr Tyr Asp Met Val Gly Ile Gln Gly Ser Asp Ser
 210 215 220
 Val Phe Ser Gly Phe Leu Leu Phe Pro Asp
 225 230

 <210> 441

248

<211> 97
 <212> PRT
 <213> Homo sapiens

<400> 441
 Gly Phe Thr Leu Trp Gly Ser Glu Tyr Ser Trp Asn Trp Asn Ala Ile
 1 5 10 15
 Asp Glu Gly Pro Lys Arg Asp Ile Val Lys Glu Leu Glu Val Ala Ile
 20 25 30
 Arg Asn Arg Thr Asp Leu Arg Phe Gly Leu Tyr Tyr Ser Leu Phe Glu
 35 40 45
 Trp Phe His Pro Leu Phe Leu Glu Asp Glu Ser Ser Ser Phe His Lys
 50 55 60
 Arg Gln Phe Pro Val Ser Lys Thr Leu Pro Glu Leu Tyr Glu Leu Val
 65 70 75 80
 Asn Asn Tyr Gln Pro Glu Val Leu Trp Ser Asp Gly Asp Gly Gly Glu
 85 90 95

Pro

<210> 442
 <211> 50
 <212> PRT
 <213> Homo sapiens

<400> 442
 Ala His Ser Ala Thr Arg Phe Asp Pro Thr Trp Glu Ser Leu Asp Ala
 1 5 10 15
 Arg Gln Leu Pro Ala Trp Phe Asp Gln Ala Lys Phe Gly Ile Phe Ile
 20 25 30
 His Trp Gly Val Phe Ser Val Pro Ser Phe Gly Ser Glu Trp Phe Trp
 35 40 45
 Leu Tyr
 50

<210> 443
 <211> 28
 <212> PRT
 <213> Homo sapiens

<400> 443
 Tyr Trp Asn Ser Thr Gly Phe Leu Ala Trp Leu Tyr Asn Glu Ser Pro
 1 5 10 15
 Val Arg Gly Thr Val Val Thr Asn Asp Arg Trp Gly
 20 25

<210> 444
 <211> 309
 <212> PRT
 <213> Homo sapiens

<400> 444
 Phe His Phe Thr Asp Cys Leu Phe Phe Gly Ser Leu Met Ser Ala Thr
 1 5 10 15
 Asp Pro Val Thr Val Leu Ala Ile Phe His Glu Leu His Val Asp Pro

249

| 20 | | | | | 25 | | | | | 30 | | | | | |
|-----|-----|--------------------|-----|-----|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|
| Asp | Leu | Tyr ₃₅ | Thr | Leu | Leu | Phe | Gly ₄₀ | Glu | Ser | Val | Leu | Asn ₄₅ | Asp | Ala | Val |
| Ala | Ile | Val ₅₀ | Leu | Thr | Tyr | Ser ₅₅ | Ile | Ser | Ile | Tyr | Ser ₆₀ | Pro | Lys | Glu | Asn |
| Pro | Asn | Ala | Phe | Asp | Ala ₇₀ | Ala | Ala | Phe | Phe | Gln ₇₅ | Ser | Val | Gly | Asn | Phe ₈₀ |
| Leu | Gly | Ile | Phe | Ala | Gly ₈₅ | Ser | Phe | Ala | Met ₉₀ | Gly | Ser | Ala | Tyr | Ala ₉₅ | Ile |
| Ile | Thr | Ala | Leu | Leu | Thr | Lys | Phe | Thr ₁₀₅ | Lys | Leu | Cys | Glu | Phe ₁₁₀ | Pro | Met |
| Leu | Glu | Thr ₁₁₅ | Gly | Leu | Phe | Phe | Leu | Leu | Ser | Trp | Ser | Ala ₁₂₅ | Phe | Leu | Ser |
| Ala | Glu | Ala | Ala | Gly | Leu | Thr ₁₃₅ | Gly | Ile | Val | Ala ₁₄₀ | Val | Leu | Phe | Cys | Gly |
| Val | Thr | Gln | Ala | His | Tyr ₁₅₀ | Thr | Tyr | Asn | Asn | Leu ₁₅₅ | Ser | Ser | Asp | Ser | Lys ₁₆₀ |
| Ile | Arg | Thr | Lys | Gln | Leu ₁₆₅ | Phe | Glu | Phe | Met ₁₇₀ | Asn | Phe | Leu | Ala | Glu ₁₇₅ | Asn |
| Val | Ile | Phe | Cys | Tyr | Met | Gly | Leu | Ala ₁₈₅ | Leu | Phe | Thr | Phe | Gln ₁₉₀ | Asn | His |
| Ile | Phe | Asn ₁₉₅ | Ala | Leu | Phe | Ile | Leu | Gly ₂₀₀ | Ala | Phe | Leu | Ala ₂₀₅ | Ile | Phe | Val |
| Ala | Arg | Ala | Cys | Asn | Ile | Tyr ₂₁₅ | Pro | Leu | Ser | Phe | Leu | Leu | Asn | Leu | Gly |
| Arg | Lys | Gln | Lys | Ile | Pro ₂₃₀ | Trp | Asn | Phe | Gln | His ₂₃₅ | Met | Met | Met | Phe | Ser ₂₄₀ |
| Gly | Leu | Arg | Gly | Ala | Ile ₂₄₅ | Ala | Phe | Ala | Leu | Ala ₂₅₀ | Ile | Arg | Asn | Thr ₂₅₅ | Glu |
| Ser | Gln | Pro | Lys | Gln | Met ₂₆₀ | Met | Phe | Thr ₂₆₅ | Thr | Thr | Leu | Leu | Leu ₂₇₀ | Val | Phe |
| Phe | Thr | Val ₂₇₅ | Trp | Val | Phe | Gly | Gly ₂₈₀ | Gly | Thr | Thr | Pro | Met ₂₈₅ | Leu | Thr | Trp |
| Leu | Gln | Ile | Arg | Val | Gly ₂₉₅ | Val | Asp | Leu | Asp | Glu | Asn ₃₀₀ | Leu | Lys | Glu | Asp |
| Pro | Ser | Ser | Gln | His | | | | | | | | | | | |

<210> 445

<211> 94

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (22)

<223> Xaa equals any of the naturally occurring L-amino acids

250

<400> 445

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Met | Glu | Val | Gly | Val | Cys | Val | Glu | Ala | Tyr | Arg | Gln | Glu | Ala | Glu |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |
| Thr | His | Arg | Arg | His | Xaa | Asn | Ser | Ala | Phe | Met | Thr | Phe | Val | Val | Leu |
| | | | 20 | | | | | 25 | | | | | 30 | | |
| Asp | Ala | Asp | Asp | Gln | Pro | Gln | Leu | Leu | Pro | Trp | Ile | Arg | Pro | Gln | Pro |
| | | 35 | | | | | 40 | | | | | 45 | | | |
| Gly | Asp | Gly | Glu | Arg | Arg | Tyr | Arg | Glu | Ala | Ser | Ala | Arg | Lys | Lys | Ile |
| | 50 | | | | | 55 | | | | | 60 | | | | |
| Arg | Leu | Asp | Arg | Lys | Tyr | Ile | Val | Ser | Cys | Lys | Gln | Thr | Glu | Val | Pro |
| 65 | | | | | 70 | | | | | 75 | | | | | 80 |
| Leu | Ser | Val | Pro | Trp | Asp | Pro | Ser | Asn | Gln | Val | Tyr | Leu | Ser | | |
| | | | | 85 | | | | | 90 | | | | | | |

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/05064

Box I - Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Claim 23 is directed to a product of the method of claim 20. Claim 20 is not a method for the production of a product, but a process for the detection for the detection of a substance. Hence, no meaningful search can be carried out.
2. ☐ Claim Nos.: 23
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/05064

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C12N 15/11, 15/12, 15/00, 15/63, 15/00; A61K 38/17, 38/16; C07K 16/00; C12P 21/02; C12Q 1/68; G01N 33/68
US CL : 536/23.1, 23.5; 435/320.1, 440, 252.3, 69.1, 6, 7.1; 530/350, 387.1; 514/12

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 536/23.1, 23.5; 435/320.1, 440, 252.3, 69.1, 6, 7.1; 530/350, 387.1; 514/2

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| X | SIMMEN et al, Gene number in an invertebrate chordate, <i>Ciona intestinalis</i> , Proc. Natl. Acad. Sci. USA, Vol. 95, pages 4437-4440, see entire document. | 1, 2, and 5-16 |



Further documents are listed in the continuation of Box C.



See patent family annex.

| | | |
|---|--|---|
| <p>* Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> | | <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&" document member of the same patent family</p> |
|---|--|---|

Date of the actual completion of the international search

12 July 2002 (12.07.2002)

Date of mailing of the international search report

02 AUG 2002

Name and mailing address of the ISA/US

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